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THE QUARTERLY REVIEW of BIOLOGY

ANIMAL VIRUSES AND EMBRYOS

BY JAMES D. EBERT AND FRED H. WILT

Department of Embryology, Carnegie Institution of Washington, Baltimore 5, Maryland

and

Department of Biology, Purdue University, Lafayette, Indiana

ABSTRACT

This review illustrates the thesis that the concepts and techniques of animal virology may provide effective measures for analyzing genetic and epigenetic relations in developing cells. The authors discuss first the effects of introducing nucleic acid in the form of virus on the subsequent history of a cell, paying particular attention to the modification of patterns of differentiation and growth by tumor viruses. The question, can viruses be used to study the origin of differences in cell specific properties, is approached by examining the pathologic effects of viruses on embryos. The role of viruses as causative agents in congenital malformations is considered. Viruses are not only agents for modifying the course of development and for detecting when differences arise in cells. Experiments from several disciplines are discussed which focus on the concept of recombination between vertebrate somatic cells. Can intercellular transfer of subcellular units modify patterns of synthesis in embryonic cells? Among the examples treated are the transfer of enzyme forming capacity by epigenetic recombination in bacterial and vertebrate cells; transfer of antibody forming capacity; the selective uptake and exchange of subcellular particles in the chick embryo; and the use of viruses to facilitate transfer of information between vertebrate cells. Finally the application of recent genetic findings, arising from virological and other microbiological studies, to the ontogeny of one class of specific proteins, antibodies, is explored.

INTRODUCTION

ART does not reproduce the visible; rather it makes visible. A tendency toward the abstract is inherent in linear expression: graphic imagery being confined to outlines has a fairy-like quality and at the same time can achieve great precision. The purer the graphic work—that is, the more the formal elements underlying linear expression are emphasized—the less adequate it is for the realistic representation of visible things." These lines by Paul Klee express the dilemma of students of genetics and embryology, who, in attempting to translate their knowledge of interactions at the cell and tissue level to the molecular level, have been forced to reproduce the visible—to redescribe the genetic material in terms of nucleic acids and differentiation in terms of specific proteins. Until recently this enforced preoccupation with chemical description has widened—rather than narrowed—the gap between genetics and embryology. But, as we begin to resolve the structures and mechanisms of synthesis of nucleic acids and proteins, we see that to *make visible* the

mechanisms of differentiation will require that increasing attention be paid to the interactions of genetic and epigenetic systems. Here we employ the distinction advanced by Nanney (1958): rather than the geographical dichotomy of nucleus and cytoplasm, it is proposed that the invariant determinants of the cell, wherever they may be located, be called genetic, and the variant determinants of cell fate be called epigenetic. Genetic in this sense refers to a specific nucleotide sequence, while epigenetic refers to the modifiable machinery, whatever its chemical constitution, carrying out the orders of the invariant nucleotide alphabet.

It is no longer meaningful to speak of resolving the apparent contradiction between genetic constancy and the orderly establishment of populations of specialized stable cells. Is there any doubt that a more effective working hypothesis states that there are differential heterocatalytic activities of genetic materials depending on the type of cell in which they are located? There can be no doubt that the same set of chromosomes may have a different appearance in different kinds of cells; nor can we question the statement that all of the genetic material may not be functioning simultaneously. Taken as a whole, the evidence suggests that we should search for the chemical basis of such differential heterocatalysis, and perhaps even for differences in the genetic material itself. In turn, the differential physiological activity of the genetic material must reflect its interaction with epigenetic components and with their products—the epigenetic elements themselves being an expression of the heterocatalytic activity of the genetic material.

The basic questions to which we seek answers are the following: how does the genetic depot change during development? To what extent are its autocatalytic functions truly conservative and its heterocatalytic activities subject to regulation? What is the epigenetic depot? How is it influenced by genetic and environmental elements, and how does it in turn influence the genetic material?

The key concept in the questions just posed is the nature of information, genetic and epigenetic, in development. It is nearly a truism that the techniques and concepts of microbiology—the use of clonal lines of cells, enzyme induction and repression, steady-state mechanisms—are applicable to studies of embryonic development. As Markert (1958) put it, "Such mechanisms offer exciting prospects for analyzing chemical processes in developing embryos, although the four-dimensional web of events that constitutes embryonic development is far more complex than the metabolic patterns studied so successfully in microorganisms." Perhaps the virus, almost literally a packet of information (nucleic acid), presents some novel and searching ways of approaching these questions in developing cells. It is the purpose of this review to illustrate this possibility—the study of genetic and epigenetic relations in developing cells with the use of viruses. But we shall borrow examples and ideas from other disciplines, particularly immunology, when they are fitting. First, we intend to discuss the effects of introducing nucleic acid in the form of a virus on the subsequent history of a cell, paying particular attention to host cell-virus relations in the tumorigenic viruses. Second, we propose to illustrate the thesis that the "state" of the cell affects its relations to virus introduction. Can viruses be used to detect differences in cell-specific properties and in their origin? Third, we will discuss whether the methods of virology can be used to determine directly epigenetic and genetic differences between cells by transferring information. Finally, we will explore the application of recent genetic findings, arising from virological and other microbiological studies, to the origin during development of a particular class of proteins, the circulating globulin antibodies.

MODIFICATION OF PATTERNS OF DIFFERENTIATION AND GROWTH BY VIRUSES

Less than a decade ago it was fashionable to attempt to escape from the apparent dilemma of cellular differentiation despite nuclear constancy by introducing the "self-reproducing particle." Fashions come and go, and in the absence of compelling evidence for the existence of such plasmagenes (to use what is perhaps the most innocuous term) in the eggs and embryos of multicellular animals it is no longer fashionable to postulate that there exist in those forms extranuclear factors having genetic continuity. The question of the role of plasmagenes in differentiation has been discussed less frequently of late, and there is nearly a plethora of reviews of the subject already at hand (Beale, 1954; Caspari, 1948; Darlington, 1944; Eph-

russi, 1953; Sonneborn, 1950; Waddington, 1956; Wright, 1945). Convincing evidence is available for the action of viruses or virus-like particles, e.g. *kappa*, the killer factor in *Paramecium* (Sonneborn, 1950), and *sigma*, the so-called "genoid" which confers CO_2 sensitivity in *Drosophila* (L'Heritier, 1948, 1951), and for the role of cytoplasmic entities in higher plants (Imai, 1937; Rhoades, 1946). Ephrussi (1953) has treated the evidence for particulates associated with inheritance in yeast, and in a separate category one may catalogue the comparatively large particles which exist in some forms and which are endowed with genetic continuity; kinetosomes and the like (Lwoff, 1950).

One logical and popular alternative to the unequal distribution of cytoplasmic genetic units (plasmagenes) is the steady-state hypothesis (Delbruck, 1949; Hinshelwood, 1952, 1953), which posits that minute intracellular or extracellular environmental changes shift the steady-state balance of enzymes and metabolites so that new phenotypic qualities appear and persist (cf. Waddington's canalization hypothesis). Perhaps the barrage phenomenon in *Podospora*, serotypes in *Paramecium*, "pokey" in *Neurospora*, and the plasmon characteristics of *Epilobium* represent phenomena of this type (Caspari, 1948; Nanney, 1958). Certainly the action of low concentrations of β-galactosides on *Escherichia coli* in creating persistent phenotypic heterogeneity in a genetically homogeneous population is an interesting model for proposals of this sort (Novick and Weiner, 1957). The evidence for the particulate (as opposed to the steady state) theory is not compelling. We would be remiss if we did not emphasize that the role of plasmagenes and "infectious" particles in differentiation and in embryonic induction has not been subjected to critical test, admittedly a difficult job. The virus bears a formal similarity to the so-called plasmagene: perhaps this discipline can suggest some new approaches to the developmental biologist. Then, too, one need not argue for a theory of differentiation based on the existence of virus-like particles to employ the ideas and techniques of virology in exploring developmental mechanisms. For example, an understanding of the mechanisms whereby a tumor virus interacts with the machinery of the host cell should contribute to our understanding of the organization of the machinery itself. One of the most effective tools of the embryologist has been the recombination experiment—at tissue, cell, and now nuclear levels; is there any reason to exclude the exchange of cytoplasmic units, whether genetic or epigenetic (cf. Kopac, 1957)? The mounting evidence for the role of the microsome in protein synthesis, including the net synthesis of protein in vitro, raises the intriguing possibility of exchanging protein-forming systems between cells not only of different somatic origin but also of different genetic origin (cf. Greengard and Campbell, 1959).

Viruses Producing Neoplasms

Beard (1958) has emphasized that virus tumors comprise the only naturally occurring tumors of known and specific etiology. Infection with the specific virus leads to multiplication of affected cells, associated with invasion of contiguous tissues and metastasis, resulting ultimately in the death of the host. Viruses have been implicated clearly in at least six major categories of tumors: the avian leukosis complex (which includes lymphomatosis, myeloblastosis, and erythroblastosis), avian sarcoma, amphibian renal sarcoma, mammalian papillomatosis, and the mouse leukemia-polyoma complex (Beard, 1958; cf. Dawe, Law, and Dunn, 1959; Eddy, Stewart, Stanton, et al., 1959; Furth, 1959). The tumor viruses do not appear to differ fundamentally from other viruses. At least two of these viruses, those of avian myeloblastosis and papillomatosis, have been obtained in homogeneous preparations. It may be significant that these viruses are present in unusually high concentrations in the tissues from which they were separated; the nature of the starting materials, plasma and keratinized papilloma, makes purification relatively straightforward. In general, the relative ease or difficulty with which virus can be separated from other tissue components is a function of (1) the stability of the virus; (2) the nature and degree of cellularity of the source; and (3) the total mass of virus in relation to other extractable components. With viruses other than the two aforementioned ones, e.g., the Rous sarcoma virus, the major problem is that of separating a small amount of labile virus from large amounts of nonviral constituents.

We do not propose to pursue the possible implications of the findings with animal tumors

with respect to human tumorigenesis, nor do we wish to consider in detail questions of susceptibility as related to age, conditioning, and genetic constitution of the host. Rather we intend to emphasize the pattern of tumor cytogenesis and histogenesis in relation to viral infection.

Fowl Sarcomas. The avian sarcomas are a system of tumors, usually considered separately from the avian leukosis complex. Among the forms of the sarcomas are spindle cell sarcomas, myxomatous growth, bone tumors, osteochondrosarcomas, and endotheliomas. Beard (1958) has listed at least 18 virus-induced tumors of "mesodermal origin," stating that "in every case the virus extracted induced the same kind of growths in the new susceptible host."

To set the stage for our discussion, let us examine the sequence of changes following inoculation of the chorioallantoic membrane with the Rous sarcoma virus. We do so not only because the chicken sarcoma was one of the first virus induced tumors to be discovered (Fujinami and Inamoto, 1911; Rous, 1911) or because it serves as a baseline for understanding some of the specific experiments to be described, but also because the description—put here as simply as possible—points up the need for understanding the mechanisms of integration of the virus into the cell, where, once integrated, it influences the course of differentiation. The chorioallantoic membrane of an 11- or 12-day-old chick embryo is composed of an ectodermal component having one to two layers of flattened cuboidal cells and a mesodermal layer containing a myxoid stroma consisting largely of loosely packed fibroblasts. Within 24 hours after the inoculation of the Rous sarcoma virus, the ectoderm becomes hyperplastic, varying from two to five cell layers in thickness. The cells themselves are basophilic, having large nucleoli. At this time the underlying mesoderm is unchanged except for the rare occurrence of basophilic round cells. But, just one day later, the mesoderm begins to change: foci of basophilic round cells with large nucleoli accumulate subjacent to the ectoderm (cf. Loomis and Pratt, 1956). The thickness of the ectoderm increases to as many as eight cell layers. Some seven hours later, the maximal extent of ectodermal proliferation (some 12 to 20 cell layers) coincides with evidence of neoplastic proliferation in the mesoderm. By 81 hours, the ectodermal cells have become necrotic, and the mesoderm is composed strikingly of fibroblastic and round neoplastic cells which by 103 hours produce reticulin fibers. Within only five days, sarcomatous cells occupy the entire mesoderm (Haddow, 1933; Keogh, 1938; Levine, 1939; Prince, 1958a, b, and c, 1960a and b; Rous, 1911).

From this brief account, one point may be emphasized. At first each lesion on the chorioallantois is composed exclusively of ectodermal cells; shortly thereafter, malignant mesodermal proliferation can be seen at the base of each ectodermal mass. Two distinct types of cells are affected by the same virus. According to Rubin (1955, 1957), it has been established that the virus has not undergone mutation. Thus the type of effect appears to depend on the type of cell infected. Rubin (1960a) in analyzing the assay of Rous sarcoma cells in vitro by the infective center technique, points out that at any given moment only a fraction of chick embryo cells are competent to support virus growth; this competence is determined by cyclical changes in the physiological condition of the cells rather than by their embryological or genetic origin. The question of cellular competence to support viral multiplication is complex, however. The precise conditions of the experiment must be kept in mind. Prince has recently analyzed a strain of Rous sarcoma virus which infects a much higher proportion, perhaps all, of the cells exposed to virus (1960a). The recent demonstration by Rubin of the widespread occurrence in chick tissue of a virus which is similar to lymphomatosis and which induces resistance to infection with Rous sarcoma virus may eventually lead to a solution of the question of competence in this system (1960b).

We are led to inquire also concerning the mechanisms of production of hyperplastic and differentiative changes. It will be well to admit at the outset that we are only beginning to understand the cytopathology of virus infections (Love, 1959); at the same time we are making rapid strides toward an appreciation of the quantitative relations between tumor viruses and host cells, owing largely to Bryan's insistence on quantitative data amenable to statistical analysis (1946a and b, 1955, 1956, 1958), Rubin's (1955, 1957) and Prince's (1948a, b, and c) quantification of Keogh's (1938) chorioallantoic membrane assay, and the recent strik-

ing success in studies of specificity of infection of the Rous sarcoma virus in vitro (Rubin and Temin, 1958, 1959; Temin and Rubin, 1958, 1959).

Although different strains of chickens vary widely in the proportion of embryos reacting to Rous sarcoma virus inoculated on the chorioallantoic membrane, and in the uniformity of response exhibited by those embryos that do react, virus assays with a high degree of accuracy can be obtained if emphasis is placed on selecting a susceptible strain of chicken that is inbred sufficiently to insure a high incidence of tumor formation.

Carr (1953) demonstrated that upon injection of the Rous sarcoma virus into adult chickens, the virus disappeared for as long as 70 hours; after 16 hours, for example, only 1 percent of the infective units of the inoculum could be recovered. In the chick embryo, virus growth curves show that 95 to 99 percent of inoculated virus is lost within 3 to 4 hours after inoculation (Prince, 1958c). These findings and others indicate that the disappearing virus has become noninfectious during the early phase of its growth cycle. Harris (1954, see also Prince, 1958c; Rubin, 1955) demonstrated that the majority of infectious units become unavailable to antibody within three hours after inoculation, the rate of loss of virus being compatible with the rate of adsorption of virus to cells. Moreover, the rate of disappearance is far greater than the rate of thermal inactivation. Prince (1958c) states also that when the virus is simply ground with fragments of chorioallantoic membrane, the virus can be recovered, indicating the absence of inhibitory materials. The eclipse period in the chick embryo has been put at 15 to 16 hours (Prince, 1958c), and 48 hours (Harris, 1954), and in chick brains, 1 to 2 days (Groupé, Rauscher, Levine, et al., 1956). It is likely that the shorter period observed by Prince resulted from the use of high initial virus concentrations and a sensitive assay. The initial stage of virus multiplication takes place concurrently with ectodermal hyperplasia and necrosis, during which time multiplication is exponential, the rate increasing with increasing titer of the inoculum. At the time mesodermal hyperplasia is evident, the virus accumulates more slowly; the more gross the lesions are, the slower is the accumulation (Harris, 1954; Prince, 1958c).

The application of tissue culture techniques in studies of the Rous sarcoma virus is not new; as early as 1941 Doljanski and his associates (Doljanski and Tenenbaum, 1942; Halberstaedter, Doljanski, and Tenenbaum, 1941; Tenenbaum and Doljanski, 1943) had attempted to analyze the cellular composition of "pure cultures" of sarcoma cells. Subsequently Sanford, Likely, Bryan, and Earle (1952) and Manaker and Groupé (1956) demonstrated focal infection of fibroblasts in vitro. Rubin (1955, 1957) first combined the chorioallantoic membrane technique with culture and cell-counting methods in his study of the production of virus by Rous sarcoma cells. Cell suspensions prepared from tumors maintained in the chick wing were cultivated according to the techniques of Dulbecco and Vogt (1953). Rubin was able to show, through a consideration of the relation between virus concentration and the number of tumors formed on the chorioallantois, that one virus particle is adequate to initiate tumor development. Hence the virus found in each tumor should represent a pure clone, barring mutation. A study of the rate of virus production by sarcoma cells in suspension showed that extracellular virus increased at a linear rate up to 6 hours, the rate being one tumor-forming unit per 100 cells per hour. The release time was found to be about 30 minutes. In contrast to the production of temperate phage in large populations of lysogenic bacteria the virus is produced, not in large quantity by a few cells, but in a slow trickle by a relatively large fraction of the cells in vitro. It may be important to point out here that a single Rous sarcoma cell in a microdrop can yield virus, divide, and then yield more virus (Temin and Rubin, 1958, 1959). The virus appears to play a direct and continuing role in perpetuating the cell in its malignant state.

Rubin and Temin (1958, 1959; Temin and Rubin, 1958, 1959) have provided further evidence of the intimate relationship between cell and virus in a series of experiments employing chick fibroblasts in vitro, the technique of Dulbecco and Vogt (1952b; 1953) being employed to grow clones of chick fibroblasts and Rous sarcoma cells and to assay the number of virus units in cell-free preparations. The findings demonstrate that fibroblasts are transformed into monocyte-like cells, which grow in grapelike clusters. Curiously, a maximum of about 10 per cent of cells in a population of fibroblasts can be in-

fected at any one time. Virus is released quickly from infected cells, being detected in the extracellular fluid within 10 to 14 hours. It is argued, however, that reinfection by newly released virus does not play a significant role in the early increase in number of sarcoma cells, the virus being passed to both progeny during cell division. Once the information is assimilated, however, further cell division is not required for virus production. Although the evidence advanced proves that the virus is heritable, at least for the relatively brief periods studied, it falls short of establishing that the virus is incorporated into the genome of the host cell, a fact which can be established only by recombination experiments. Care must be exercised even in the latter approach to determine whether the virus has become associated closely with the host's genome or whether it is episomic. (An episome is a genetic element which may exist alternatively as an autonomous unit independent of the chromosome, or attached to the chromosome.) A word of caution must be voiced in connection with studies of morphological mutants, for to a surprising degree the morphological manifestations of the tumor viruses depend on the age and constitution of the host cells, a subject treated again on pp. 275–276. Temin (1960) has shown that different variants of Rous sarcoma virus can be obtained which transform the same clone of fibroblasts into strikingly different morphological states, a clear example of the far-reaching effects of externally applied (viral) RNA on epigenesis. Moreover, we are confronted with the pressing unresolved problems of the degree of relationship between virus and normal tissue components and between tumorigenic viruses. Prince (1960b) has argued effectively for the presence of a high percentage of cells in the Rous sarcoma which do not release infective virus, yet contain virus and resist superinfection. We need only mention the evidence for antigenic kinship not only among the sarcomas (Rous sarcoma number 1, Fujinami myxosarcoma, etc.) but between the Rous sarcoma virus and lymphomatosis and myeloblastosis viruses. Eckert, Sharp, Beard, Green, and Beard (1955) have demonstrated a close immunological relationship between avian erythromyeloblastic leukosis virus and normal tissue components.

Genetic studies of the animal viruses have followed the procedures and ideas of bacteriophage genetics. The existence of strain changes on passage in different hosts suggested that mutation and selection operate in virus populations. In the 1940's Burnet demonstrated the presence of stable recombinant types from mixed infections of influenza in the egg; later work on influenza and vaccinia has verified the existence of recombination (reviewed, Burnet, 1958). Fenner and Combden (in Burnet, 1958) have examined six characters in two vaccinia strains; they have shown a high proportion of recombinant types following mixed infection. Ultraviolet-irradiated virus also can contribute to recombinant types. Gottlieb and Hirst (1954) have shown that phenotypic mixing occurs in progeny from mixed infections. The isolation of mutant strains of polio with reduced pathogenicity and changed pH sensitivity offer hope that more refined genetic studies will be forthcoming. The Berry-Dedrick transformation (1936) has been cited frequently as providing evidence that transformation can occur between animal viruses. Infection of rabbits with fibroma virus and heat-killed myxoma leads to myxomatous lesions. The great variability in this system has left much to be desired. Now, Fenner, Holmes, Joklik, and Woodroofe (1959) have suggested that the findings are due not to transformation but to reactivation of myxoma virus.

It has been suggested also that the results of Gye and Purdy (1931) on inactivation (when assayed in ducks) of Fujinami sarcoma virus grown in the chick, by antiserum against normal chick tissues is evidence for incorporation of host material into the virus and possible transduction. Rubin (1956), however, has shown in experiments with Rous sarcoma virus that most if not all of a similar effect is due to action of the antiserum and complement on host cells of the animal used for titration, a finding supported by experiments of Borsos (1958). Habel, Hornibrook, Gregg, Silverberg, and Takemoto (1958) also have demonstrated that the effect of anti-cellular serum on the inhibition of multiplication of a number of viruses, as measured by inhibition of cytopathogenicity in vitro, may be explained by action on the cells, support for Rubin's point of view. Yet all of these experiments differ from the experiment of Gye and Purdy, which is interesting enough to warrant careful repetition in the same system.

Mouse Leukemias. Following the discovery of the virus-induced breast cancer of mice (Bittner,

1936, 1948), it was 15 years before Gross (1951) reported that it was possible to induce the subsequent appearance of leukemia by inoculating newborn mice with cell-free extracts from certain kinds of leukemias. Kaplan (1959) and Burnet (1959a) have summarized the main features of mouse leukemia, the following points being pertinent to this discussion. (1) Different strains of mice differ widely in spontaneous incidence, and in the ease with which agents can induce leukemia. (2) Agents as diverse as ionizing radiation and estrogens increase the incidence of the disease, usually lymphocytic leukemia. (3) As noted above, the disease can be propagated by cell-free extracts provided newborn hosts are used. Friend (1957) (see also Buffett and Furth, 1959) has observed that a myelogenous leukemia, that bears no relationship to lymphoid tumors, can be transmitted in Swiss mice by cell-free preparations. (4) Virus-like inclusions have been observed in electron micrographs of many tumors and leukemic cells. (5) Kaplan has postulated an indirect mechanism of radiation-induced leukemia formation to account for his findings that first, the thymus appears to be necessary for the induction of leukemia, and second, that tumors appearing in thymectomized irradiated mice grafted with normal thymus arose in the grafted thymus, some of them being of the donor type.

Burnet, who approaches the problem of leukemia from the point of view of clonal selection of mutated cells, asks whether the evidence available eliminates the general idea of somatic mutation. In particular, he argues that "the essential feature [of cancer] is that finally a population of cells emerges which can be shown to be *genetically* different from normal lymphocytes by their capacity to produce disease in isologous hosts. We know of no way by which *genetic* change can occur other than by somatic mutation. . . ." (italics added). We may ask why Burnet adopts the somatic mutation hypothesis rather than the hypothesis that leukemia is a virus-induced tumor. He believes that no virus could conceivably survive in nature if it were limited to genetically homozygous hosts, and points out the "air of biological unreality about much mouse leukemia work, because all transmission experiments are by parenteral inoculation in pure strains of mice." Burnet describes the leukemia agents as "operational" viruses, and conjectures that they are either viruses which in most strains produce no symptoms but which can disturb some control in unstable strains (he interprets the mouse mammary cancer factor along this line) or subcellular units genetically of host origin. Burnet then goes on to stress the latter possibility, which brings his argument into line with the postulates of many investigators who have sought to relate viruses to the modification of normal subcellular units. One must agree with Burnet that the numerous experimental studies now in progress of the induction of neoplasms by nucleic acids and nucleoproteins should clarify the question, but at the same time we may ask whether emphasis on clonal aspects need lead necessarily to emphasis on somatic mutation (cf. Kaplan, 1959; Rous, 1959). In fact such emphasis appears unwarranted. It must be stated also that the limitation of leukemias and other virus-induced tumors to genetically homozygous hosts may be less a limitation of the viruses than of the scope of the experiments in which they were employed, as a consideration of the mouse leukemia—mouse polyoma complex makes abundantly clear.

The difficulties encountered in distinguishing whether neoplasms produced in several organs of the same animal are the result of multiple effects of one agent, of a small number of viruses, or of a large family of viruses, may also be illustrated by considering the leukemia—SE polyoma virus "complex." One of the more remarkable recent developments has been the production of a spectrum of tumors and lesions ranging from pleomorphic tumors of mucous glands (parotid, submaxillary, etc.) to mammary adenocarcinomas, sarcomas, and kidney tubule lesions following inoculation of fluids from cultures of mouse tissues carrying lymphocytic leukemia into newborn mice, rats, and hamsters (Eddy, et al., 1959; Stanton, Stewart, Eddy, et al., 1959; Stewart, Eddy, and Borgese, 1958). Whether the "agent," designated the polyoma virus, is, in fact, a single agent having multiple effects or whether a number of closely associated viruses are responsible is a matter of conjecture. Moreover, the relation of the polyoma virus to the lymphocytic leukemia from which it was derived originally is not clear.

According to Furth (1959), for example, it appears that the findings indicate the inclusion of a pluripotent polyoma virus distinct from the leukemia virus. It is interesting to note, how-

ever, that Kassel and Rottino (1959) have found that whether leukemia or other tumors are produced by filtrates of leukemic tissue depends in large measure on the route of inoculation, the presentation of small volumes intravenously resulting in a high incidence of leukemia. By contrast, the subcutaneous inoculation of a large volume of filtrate produces a very low incidence of leukemia. And finally, the relation of the filtrate-induced leukemias to spontaneous leukemias remains to be resolved. For example, Dawe, Law, and Dunn (1959) failed in attempts to isolate a leukemia-inducing agent, yet found that cell-free filtrates of lymphocytic leukemia, described earlier (Gross, 1951, 1957), produced parotid tumors. Rowe, Hartley, Brodsky, and Huebner (1958), who employed complement fixation tests with tissue-culture antigens, found that the polyoma virus is unrelated serologically to a wide variety of known viruses, including the Bittner milk agent (Bittner, 1936, 1948) and the hematopoietic tumor-inducing virus described by Friend (1957). Mice with filtrate-induced parotid tumors or leukemias were invariably positive for presence of antipolyoma antibody, but mice with spontaneous leukemias were negative.

Finally, we must cite the observations by Gross (1959) that a filterable leukemic agent recovered from C_3H mice in which leukemia was induced by X-irradiation can be passed serially into suckling C_3H mice, and by Kaplan (1959) that the injection of cell-free filtrates from radiation-induced thymic lymphosarcomas into isologous newborn mice results in thymic lymphosarcomas. These observations and those on the polyoma system reenforce the contention that, considering the question of the relation of "latent" virus to subcellular particles of host origin, care must be exercised in formulating a rigid concept of autonomous subcellular units. Increasing attention must be paid to the initial steps in carcinogenesis as revealed, for example, by Rogers' (1957) studies of the formation of carcinogenic intermediates within a few hours after the administration of urethane (cf. Smith and Rous, 1945). The fact remains that we have not begun to exploit the techniques of clonal analysis in vitro in studying the leukemias; yet there is good reason to believe that once the technical difficulties in culturing hematopoietic cells in vitro are mastered, the availability of well-defined genetic markers in inbred mice should make for rapid progress. It is encouraging that Beaudreau and his associates (1959) have described a system for maintaining continuous cultures of leukemic cells from myeloblastic chickens. Osgood (1959) has summarized effectively the most pertinent information on survival of blood cells in vitro.

Latency

Dulbecco (1958) has proposed that animal viruses be subdivided into three groups on the basis of virulence. Moderate viruses are those which interact with the nucleic acids of the host cell, the virus being passed to cell progeny, and which produce infectious states lasting a long time compared to the cell generation period. Submoderate viruses form an intermediate group in which cytopathologic effects appear after a delay from the time of initial infection, being followed ultimately by cell death. Virulent viruses are typical necrotic viruses, producing effects in one infectious multiplication cycle.

The tumor viruses are classed as moderate viruses. Another important subdivision of this group comprises the latent viruses, which infect and multiply in an organism or cell without yielding symptoms of disease and massive cell death. Sometimes it is implied also that the virus lies "dormant" in the cell in a masked state, but the term, *latent*, should refer only to the failure to produce cytopathologic and histopathologic effects and not to virus multiplication or the state of the virus in the cell.

We are concerned principally with the relevance of latent viruses to epigenesis, hence we shall focus attention on the cellular aspects of the phenomenon and ignore for the most part the stimulating and varied literature on subclinical and chronic latent infections. Latent infections have been suspected and invoked for many different kinds of viruses in different experimental systems, e.g., avian myeloblastosis infection in vitro, adenovirus in vivo and in vitro, lymphocytic choriomeningitis in mice, foot and mouth disease, rabbit papillomatosis, herpes simplex, mumps, and Newcastle disease virus, to name some of the more recent examples. Explanations for latency or apparent latency have ranged from attempts to compare latency with lysogeny (cf. Andrewes, 1958) in bacteria to the existence of circulating inhibitors (Bryan, 1958; Ginsberg, 1958; Ho and Enders, 1959).

The classical example of latent virus infection is herpes simplex. Infection of the newborn leads to stomatitis and diarrhea. Upon recovery from the disease, subjects may continue to harbor the virus for their entire lifetimes, the virus causing periodic outbreaks of cold sores about the mouth, especially during periods of emotional and physical crisis (Burnet and Lush, 1939). Characteristic deoxyribonucleic acid (DNA) inclusion bodies are observed in the cell nucleus. Even in this oft-cited case the evidence for latency at the cellular level is not as critical as one might hope. Stoker (1959; Stoker and Newton, 1959) has grown and assayed this virus in HeLa cell cultures, demonstrating in single cell studies that the virus stops cell division immediately and kills the cells (cf. Wheelock and Tamm, 1959). However, stable, virus-producing cultures may persist indefinitely even when grown in the presence of antiserum. The cell populations show only a small percentage of cells that support viral growth at any one time, and Stoker suggests that a stable equilibrium of virus production, cell death, and cell multiplication produces an apparent latency on the tissue level. However, Scott and McLeod (1959) have demonstrated that different strains of herpes may produce different effects; a strain similar to that used by Stoker leads to breakdown of cell boundaries, cell death, and syncytium formation; but another variant produces a definite proliferative response and a piling up of cells accompanied by very little necrosis. There is still some doubt, then, as to the ability of some varieties of herpes to remain in stable association with a cell throughout cell division without killing it.

The evidence for the adenoviruses also is inconclusive. These viruses were isolated originally from tonsils and adenoids of apparently normal children, but of the 14 antigenic types now recognized a few are known etiologic factors in some respiratoroy diseases (Huebner, 1958; Rowe, Huebner and Bell, 1957). Extensive studies by Ginsberg (1958a and b; see also Pereira, Allison, and Balfour, 1959) have shown that the virus propagates and causes extensive inclusions in the cell nucleus. But even when the cytopathology (in 48 hours with variety 4) is becoming extensive only 1 percent of the cells have released virus, and cell death does not seem to be extensive. It will be difficult to determine if these viruses meet Dulbecco's criteria for moderate viruses until virus release from single cells has been studied.

Vogt and Dulbecco (1960) have recently examined infection of mouse embryo and hamster cell cultures with PY polyoma virus. Their evidence suggests that the virus may "transform" the cell into a state where an integrated virus-host cell relationship of the moderate type may persist. Examination of this system certainly deserves further study.

Several attempts have been made to demonstrate latent infection at the cellular level by selecting resistant cell populations in vitro after successive challenges with virus. Vogt and Dulbecco (1958a and b) have isolated a clone of HeLa cells showing increased resistance to polio virus; it is interesting that the chromosome idiograms of the resistant cells show marked differences when compared with the parent stock. Some of the experimentally produced sublines may show continuous production of virus without destruction of the cultures. These workers feel no cogent evidence for permanent virogenicity of the cells has been obtained and that the phenomenon is the result of the selection of genetically different cells. Henle and associates (Deinhardt, Bergs, Henle, and Henle, 1958; Henle, Deinhardt, Bergs, and Henle, 1958; Henle, Henle, Deinhardt, and Bergs, 1959) have examined in detail some strains of Lung-To and MCN cells persistently infected with mumps and Newcastle disease virus. The cells show a longer generation time, great aerobic glycolysis, and increased resistance to vesicular stomatitis virus. If the cells are cultured in specific antiserum for long periods (longer than 100 days), they may occasionally be cured; namely, they show no signs of virus production or resistance to vesicular stomatitis virus, but usually there is a gradual return of virus production and resistance to stomatitis after removal of antiserum. The Newcastle disease viruses recovered from these cultures show an altered plaque morphology on chick fibroblasts in vitro. The resistance to stomatitis virus meets the criteria for interference (cf. Isaacs, 1959); and although the proportion of cells yielding virus is quite low (1/50), the culture must be infected with at least one infectious unit per cell to confer stomatitis resistance. It appears (Henle, et al., 1959) that there must be a heterogeneous population of cells, some of which can support viral growth (single cell isolations

have not been carried out) and some which require virus to resist stomatitis virus but produce no Newcastle virus. The earlier suggestion by these workers that interferon was being produced in these cultures has recently been confirmed (Henle, et al., 1959).

An equally interesting but complex system is that reported by Puck and associates (Cieciura, Marcus, and Puck, 1957; Puck and Cieciura, 1958), who isolated a clone of HeLa cells resistant to Newcastle disease virus by repeated challenge with the virus. The resistant cells produce plaques, however, when plated on X-rayed HeLa giant cells; and subsequent analysis demonstrated that the virus (which kills the sensitive X-rayed cells) is being continuously produced by the apparently normal cells. Cultivation of the HeLa subline for 21 to 24 days in 1 percent anti-Newcastle virus serum destroyed the plaque-forming ability (it later returned), but the cells still resisted viral superinfection. Therefore, these workers feel that a genetic change in the HeLa cells is a more likely explanation than a mechanism comparable to lysogeny.

The general interpretation (Huebner, 1958) emerging from these studies on latent infections is that nothing comparable to lysogeny has been discovered, and that cell populations showing persistent infection may represent a balance of cell multiplication and death in a highly resistant and heterogeneous population. Specific antibody also may play a role in vivo (Bryan, 1958). Even failure to inhibit production of a virus with antiserum in vitro may signify only a direct cell-to-cell transmission of the virus which is not accessible to action of the serum. Isolation and study of single infected cells in microdrops is an important experiment for the interpretation of these phenomena. A stable and intimate association of virus and cell cannot be ruled out in many cases; and since careful analysis of the phenomenon is only beginning, unexpected results may follow.

The recent radiological and single cell studies of Rubin and Temin (1958, 1959; Temin and Rubin, 1958, 1959) with Rous sarcoma virus on chick embryo fibroblasts demonstrates an intimate association of cells and viruses. It was found that in microdrops single cells which release virus continuously can still undergo mitosis and release more virus, the ability to produce virus being passed to both progeny. Is this comparable to a lysogenic state? The capacity of infected cells to produce Rous sarcoma virus is more radiosensitive than is the capacity of such cells to yield a typical cytocidal virus, Newcastle disease virus. And the capacity of the bacterium to support temperate phage growth is more radiosensitive than is the capacity to support virulent phage growth.

X-irradiation of the host cells destroys the ability to support viral growth, but the dose required gradually increases from 5 to 15 hours after infection with Rous virus. These interesting experiments have demonstrated a rather stable and perhaps intimate cell-virus interaction. While some workers argue that any comparison with temperate phage must be ruled out because of the slow release of Rous virus compared with the single lytic burst of phage release, Prince (1960b) has argued effectively that the points of comparison between phage and Rous virus are extremely numerous. The difference in mechanisms of release of virus may only be due to mechanical differences in cell structure. Polio virus may well be released in a burst (Lwoff, Dulbecco, Vogt, et al., 1955).

One of the more interesting and important phenomena associated with temperate phage infection is lysogenic conversion (reviewed in Bertani, 1958), in which the presence of prophage in the cell confers on the host cell new properties which are not associated with viral multiplication. For instance, infection of *Corynebacterium diphtheria* with β phage leads to production of diphtheria toxin by the bacterium; also lysogenic bacteria show a greatly increased resistance to homologous superinfection. Certainly there are no clear cases yet reported with animal viruses of anything comparable, but suitable genetic markers do not exist in most cases for performing suitable experiments. Yet, Rogers (1959) has reported that rabbit papilloma virus causes a specific increase in arginase of tumor cells. We have already noted some examples of resistance to superinfection (Henle et al., 1958, 1959; Puck and Cieciura, 1958; Rubin, 1960b) and Rubin (1959) has invoked the comparison to lysogenic conversion to explain the finding that turkeys tolerant to normal chick tissue will develop sarcomas when challenged with Rous sarcoma virus (cf. Harris, 1956; Svoboda, 1958). One may ask, however, whether a simpler explanation is possible, namely, are chicken cells surviving in

the tolerant turkeys infected? Are the sarcomas in fact from chicken cells introduced during the prior induction of tolerance, and so involving a homologous chicken virus—chicken cell system in the turkey host? Resistance of Rous sarcoma to heterologous superinfection apparently is nonexistent (Nankervis, Gray, and Morgan, 1959). Behavior of the cells in persistently infected cultures may change (Vogt, 1958), and even the properties of the viruses from such cells may change (Takemoto and Habel, 1959).

Stable relations of virus and host cells bear a formal relation to the plasmagene hypothesis of differentiation. If the presence of virus confers new properties upon the host cell, the system becomes more than a model, but a possible mechanism of differentiation. The importance of the plasmagene hypothesis lies in the fact that here is a way to introduce a true genetic, yet extranuclear, heterogeneity. The chief difficulty from the heuristic point of view is that the hypothesis requires a pre-existing heterogeneity resulting in unequal distribution of the particles to different cell lineages. It is certainly of the utmost importance in embryology to apply techniques for detecting self-reproducing and possibly infective particles. We may learn as much about the properties of such possible agents in differentiation from studies on latent virus infections as we can from studies with embryos. Latent viruses also might be invoked to explain selective cell death in embryogenesis.

Infectious Nucleic Acids

One of the more exciting developments of present day virology is the finding that administration of pure viral ribonucleic acid (RNA) produces typical virus-induced cytopathology and histopathology of host tissues from which intact virus can be recovered. This finding may bear a comparable relation to genetics and embryology as bacterial transformation does to biochemical genetics. Transformation studies established beyond doubt that the genetic depot, at least for some characters in *Pneumococcus* and *Hemophilus*, is deoxyribonucleic acid (DNA) (See review by Hotchkiss, 1957). Recently Gierer and Schramm (1956) reported that RNA from tobacco mosaic virus is infectious, but only at extremely low titers; and studies by Fraenkel-Conrat (1956; Fraenkel-Conrat, Singer, and Williams, 1957) have shown the genetic specificity of heterologous combinations of RNA and protein from Holmes Ribgrass virus and Tobacco mosaic virus residues in the RNA. Studies on RNA from small animal viruses have now established that it conveys the information necessary for the formation of complete virus. Furthermore, of particular importance in the present context, this finding provides an experimental system and formal model for examining the effects of externally introduced RNA "information" upon the subsequent epigenetic history of the cell. What the viral nucleic acid does in bacteriophage infection, and presumably in animal virus infection, is to divert a portion of the host cell's metabolism to its own use.

The infectivity of animal virus nucleic acid was demonstrated clearly by Colter and his associates (1957, 1958). Utilizing the previous method of Gierer and Schramm (1956), the extraction of RNA by use of phenol, they found that extracts of tissue infected with polio and W. Nile encephalitis viruses were infectious (at a titer of 0.1 percent of intact virus) when inoculated into mouse brain. RNA from ascites tumor cells infected with mengo-encephalitis virus also yielded infective preparations. Virus was identified primarily with specific antisera. The RNA preparations were differentiated from intact virus by chemical analysis, action of RNAase, heat treatment, lability to NaCl, and centrifugation. Subsequently using similar procedures, Wecker and Schafer demonstrated infectivity of mouse encephalitis virus, western equine encephalitis virus, and eastern equine encephalitis virus (1959, 1957). Cheng (1958), Brown (1958a and b), and Portocala, Boeru, and Samuel (1959), also have prepared infectious RNA from Semiliki forest virus, virus of foot and mouth disease, and influenza virus, respectively. Although Colter noted cytopathologic effects of RNA preparations when they were assayed in tissue culture, these were not always reproducible. However, Alexander and associates (1958, see also Sprunt, Redman, and Alexander, 1959) demonstrated reproducible plaque formation using polio RNA and HeLa cells. Use of a hypertonic salt medium was necessary to produce extensive infection from which intact normal virus could be recovered. Holland, Leroy, and McClaren (1959) have extended these studies with RNA from type 1 polio, coxsackie A and B, and Echo 8 viruses. Utilizing

established cell lines, primary monolayers, and intact animals they demonstrated that the RNA was infective for nonprimates that normally are not susceptible to these viruses (rabbit, swine, mouse, guinea pig, chick, and hamster). Virus was released in one infective cycle without apparent cytopathologic effects. This observation suggests that in some cases the specificity of the viruses for different hosts resides in the non-nucleotide portion of the virus, presumably the serologically active outer coat which attaches to cells.

Some recent experiments, while posing difficulties in interpretation, give promise of investigating directly the eclipse phase of virus-host cell interaction. Schafer (1959) noticed that in order to prepare RNA of equine encephalitis and mouse encephalitis viruses, phenol must be added to the mouse brain before homogenization. If RNAase is added to the homogenate before phenol extraction no activity can be recovered, i.e., probably some vegetative form of the virus is furnishing the active material. Extraction of purified virus preparations yielded no infectivity, but action of hot rather than cold phenol on concentrated virus preparations released some infective RNA. Wecker (1959) has shown also that hot phenol is effective in obtaining active RNA from western equine encephalitis virus but cold phenol is not. More attention must be directed to the lipid portions of the viral structure.

Huppert and Sanders (1959) have examined infective RNA from Krebs-2 ascites tumor cells infected with encephalomyocarditis virus, assaying both with a plaque technique, in vitro, and injections into mice. They found that the cell population of the assay in vitro was presumably heterogeneous with regard to the ability to take up RNA. (A similar heterogeneity probably exists also for bacterial transformation, Rous sarcoma virus infection, herpes simplex infection, etc.). Even more surprising is the finding that the amount of infective material extracted from the cells is not proportional to their content of complete virus. If a tissue extract was centrifuged at 105,000 *g*, the virus content of the supernatant was only 1/1000 of the sediment but had all the infective RNA. In contrast to Schafer's results, the use of RNAase before extraction with phenol did not destroy infectivity. Further examination of RNA preparations of encephalomyocarditis (Hoskins, 1959) has shown that the titer obtained using different hosts is influenced by the variant of virus used and the previous cell type from which the virus was harvested, e.g., encephalomyocarditis S 180 and K-2 variants harvested from Krebs-2 carcinoma or sarcoma 37 cells showed significant titer differences when assayed on Krebs-2, Sarcoma 37, Erlich ascites, or sarcoma 180 cells.

It is interesting that all the cases of RNA infectivity have been virulent and necrotic viruses. However, Maassab (1959) (also Portocala and associates, 1959) have reported that RNA extracted from chorioallantoic membranes infected with influenza, a more moderate virus, is infective for chick kidney tissue culture cells. An extract of concentrated virus preparation was, as in Hoskins' (1959) work, not infectious. Attempts to repeat this work have thus far been unsuccessful (Simon, 1960).

Although infectivity of DNA from DNA-containing viruses like the pox group has not yet been reported, an interesting phenomenon of superficial similarity is the Berry-Dedrick transformation (1936; Smith, 1952; reviewed, Burnet, 1958). Shack and Kilham (1959) have offered presumptive evidence that the active portion of the heated inactivated myxoma is DNA, for after urea treatment, but not before, the agent is inactivated by DNAase but not RNAase. Hanafusa, Hanafusa, and Kamahora (1959) have reported also that ectromelia "transforms" heat inactivated vaccinia in L strain Earle's cells, in vitro. However, Fenner and associates (1959) have cautioned that "transformation" is a misleading word for describing these results, for it suggests something comparable to transformation in bacteria. Rather, Fenner and his colleagues have shown with variants of vaccinia and other pox viruses that something closer to recombination and reactivation are taking place. The ultimate mechanism may prove to be close to multiplicity reactivation in bacteriophage (Dulbecco, 1952a; Luria, 1947).

In contrast to the examples cited above, comparable evidence does not exist for the infectivity of nucleic acids of tumor viruses. Although the infective unit of the Rous sarcoma virus has not been prepared as pure RNA (Bryan and Moloney, 1957), Bather (1958) has shown a strong relationship between infectivity and RNA content of partially purified virus preparations. Epstein and Holt (1958) have also provided evi-

dence for the importance of RNA in Rous virus structure.

Findings of infectious DNA have not been substantiated fully. Attention has been paid to the problem, and preliminary findings are at hand which suggest that DNA prepared from leukemic tissues is infectious. but the evidence is not yet convincing (Hays, Simmons, and Beck, 1957; Latarjet, Rebeyrotte, and Moustacchi, 1958). In a brief statement, DiMayorca, Eddy, Stewart, Hunter, Friend, and Bendich (1959) have offered evidence that a purified infectious component can be isolated from a crude SE polyoma virus suspension; it is DNAase sensitive and RNAase resistant, suggesting that it may be DNA.

Although this line of work is in its infancy the "infant" is a lusty one, offering hope of a new approach for elucidating nucleic acid-cell interactions, especially the finding of an infectious viral precursor. This work has also shown a wide applicability of Gierer and Schramm's phenol method for extracting biologically active RNA. The application of this technique to obtain RNA active in development has begun (Clayton and Okada, 1959; Niu, 1958). It only remains to reiterate the need to use end points that can be measured accurately in studies on effects of nucleic acids on cell populations. For instance, recent studies of the active agent in embryonic primary induction waver between nucleic acid and protein, just as did the argument on the chemical nature of the gene. Effects of nucleic acid from one cell type on another, in vivo, are hampered by the fact that the specificity of the changes encountered is difficult to assess. While they may be few, there are some suitable tissue specific markers which can be used at present; and perhaps it is not remiss to add another plea for the use of mouse tissues, in which the genetic background can be controlled and in which a large number of specific genetic markers exist.

VIRUSES AS TOOLS FOR STUDYING THE DEVELOPMENT OF CELL AND TISSUE SPECIFICITY

Throughout the foregoing pages we have treated the animal virus as a genetic unit, stressing its infectivity and integration into the genetic apparatus of the host; we have reiterated the fashionable view that tumor viruses may become a part of the host's genetic apparatus; and along similar lines we shall stress the possible usefulness of viruses as tools in effecting incorporation of inductive nucleic acids or nucleoproteins. These ideas are attractive, yet some would argue that they have received more serious attention than is warranted by real evidence.

The same criticism cannot be directed toward the material to follow for although a part of what we shall have to say is highly speculative, the subject has received little notice; in fact one of our objectives is to direct attention to it. It seems evident that the host cell-virus relation is reciprocal: changes in the host may influence the ability of a virus to multiply and may lead to a modification of the cytopathologic effects. Viruses are sensitive indicators of some aspects of the "state" of a potential host cell. The question is raised whether viruses may prove to be useful tools in exploring the development of cell and tissue specificity. Here we refer to the pantropism, or apparent lack of cell or tissue-specificity of a number of the animal viruses in early embryos, and the changing spectrum of specificities exhibited when viruses are inoculated into embryos at progressively older stages. It is interesting to inquire also whether, preceding the pantropic stage, there may be a stage in early development when the embryo totally fails to support viral growth.

What kinds of information do we seek? We would like to know, for example, the ability of embryonic cell surfaces to provide attachment sites for viruses. Does an increasing degree of cell-virus specificity during development reflect a loss in some cells of the appropriate virus-attachment sites? Or rather does it reflect a loss in ability to support viral growth on the part of all but one population of cells? Conversely, does it reflect increasing capacity in either or both of these attributes coupled with greater "affinity" for the virus? For instance, similar considerations have resulted in the use of polio virus to distinguish differences between closely related cell lines (Murphy and Armstrong, 1959).

The pioneering observations of Rous and Murphy (1911) on the growth of the Rous sarcoma on the chorioallantoic membrane of the chick embryo, followed by the demonstration by Woodruff and Goodpasture (1931) that fowl pox virus also could be cultured on the chorioallantois, focused attention on that membrane as an uncommonly favorable site for the cultivation of viruses. We know as the result of repeated demonstrations that viruses may be propagated

not only on the chorioallantois, but also on the other extra-embryonic membranes and in the embryo itself. We do not propose to consider the practical and technical aspects of the growth of rickettsiae and viruses in the embryos; these questions have been reviewed repeatedly. For example, Cox (1952) lists in tabular form the growth characteristics and preferred sites of viruses in the chick embryo. Instead we shall take up virus infections in the embryo under two headings: (1) A survey of the pathological effects of viruses on the embryo. Our attention will be centered largely on the chick embryo, with reference to other species for comparison and emphasis. (2) Viruses and congenital malformations, in which we shall treat the question of possible changes in host-virus specificity during development, with emphasis on its relationship to mechanisms of production of congenital malformations.

Pathological Effects of Viruses on Embryos

Robertson, Williamson, and Blattner (1955) have emphasized that the character of abnormalities produced in embryonic hosts by a given virus depends on (1) the genotype and conditioning of the host and (2) the stage in development at which the virus is introduced. In the susceptible adult host each virus produces a spectrum of effects which, as we have made clear earlier, may be regarded as characteristic of that virus. Although understanding of the histopathology of infected tissues is far from complete, it is not misleading to say that for numerous viruses we have adequate descriptions of the tissue sites of infection and pathogenesis; what is lacking is information on the cytopathology of virus infection. What do we know about the intracellular activity of viruses? The internal structure of several viruses has been demonstrated, and we are gaining insight into the morphologic aspects of viral differentiation. Ahead of us lie a range of problems that include the relationship of viral "particles" to tumor formation, the nature of incomplete and latent viruses, the formation and localization of viral antigens, and the relation of virus antigens, and the relation of viruses to inclusion bodies. We are developing the techniques to answer some of these questions—electron microscopy, the application of fluorescent antibodies—but the fact remains that our knowledge of the effects of viruses on embryos remains at the level of histopathology (Enders, 1954; Love, 1959; Morgan, Rose, and Moore, 1957).

With few exceptions critical systematic studies of the effects of viruses at progressive stages in the developing embryo are yet to be undertaken. By and large, studies of the pathogenesis of viruses in the embryo have been incidental to using the embryo or its membranes as sites of propagation for other experimental purposes. Also the ease with which viruses can be cultivated on the chorioallantois at 9 or 10 to 14 days of incubation has resulted in over-emphasis on that period of development at which time the lesions often simulate those observed in the older host. Buddingh (1952) has considered several representative examples, a few of which may be cited here. When fowl pox virus is inoculated on the chorioallantois at 10 to 14 days, the membrane erupts in a pock-like lesion in which the ectoderm is affected profoundly, the endoderm to a lesser extent, and the mesoderm not at all. In the ectoderm there is hyperplasia and hypertrophy, but little tendency toward necrosis. Buddingh (1938) showed that when fowl pox was inoculated first intracerebrally in newly hatched ducks, and then recovered and passed to the membrane, it was modified in that it now affected the mesoderm dramatically. Although the fowl pox virus can be detected in the embryonic circulation, lesions in the embryo are few—and the embryos die only rarely.

The effects of fowl pox may be contrasted with those of vaccinia virus; following inoculation with the latter at 12 to 14 days, most embryos die within 72 to 96 hours. Focal proliferations are observed in the chorionic epithelium within 24 hours, and the membrane becomes ulcerated. As in fowl pox, different strains of vaccinia vary in the extent to which they affect the mesodermal and ectodermal cells. Vaccinia virus can be recovered also in the embryonic circulation; and in contrast to fowl pox, produces a striking effect on those embryos that survive, focal lesions being widespread (excepting the central nervous system). The subject is treated more fully by Buddingh (1952) who considers also cow pox, variola virus, and herpes simplex which have similar patterns of infection of the chorioallantois and generalization to the embryo. In the case of herpes simplex, the virus appears to be pantropic, with the site of primary infection depending on the route of inoculation. For example, intracerebral inoculation results in encephalitis; chorioallantoic

inoculation leads to local infection after which the virus enters the embryo by the vascular route, showing in the embryo predilection for mesodermal cells.

Rabies virus also produces effects on the embryonic nervous system (Dawson, 1933, 1941). Intracerebral inoculation of the virus in the embryo of 10 to 14 days results in destructive processes in the central nervous system. Negri bodies are observed chiefly within the cytoplasm of neurons, being common 6 to 7 days following inoculation. Both the central and peripheral nervous systems contain Negri bodies. Dawson (1933, 1941) found the virus to be restricted to nervous tissue, but Koprowski and Cox (1947) have described pantropic strains.

Little is known of the effects of tumor viruses during progressive stages of development. Perhaps the most informative studies on infection of early embryos with tumor viruses stem from the pioneering investigations of Duran-Reynals and his co-workers. As an example, let us consider the hemorrhagic disease caused by the Rous sarcoma virus. Hemorrhagic lesions in chickens with Rous sarcomas were described first by Rous and Murphy (1913). Duran-Reynals (1940) reported that the hemorrhagic lesions were more frequent in young chickens than in old; later, in collaboration with Milford (1943) he inoculated the virus intracoelomically and intravenously into chick embryos and produced only hemorrhagic disease, not tumors, in the embryos proper. Occasionally a small nodule was found on the chorioallantoic membrane at the site of inoculation. The lesions appeared to be due to destruction of endothelial cells. Lo and Bang (1955a and b), Borsos and Bang (1957), and Borsos (1958) found that the appearance of the hemorrhagic lesions was favored by the intravenous route of inoculation, the use of younger embryos, and elevated incubation temparatures. None of the embryos inoculated at day 3 showed any tumor formation; many were hemorrhagic. In contrast, many tumors were seen in embryos inoculated at day 10, and after day 12 few embryos showed any hemorrhagic lesions. Borsos and Bang (1957) have reported a quantitative relationship between the number of lesions and the amount of virus used in the inoculum.

It is hardly necessary to reemphasize the importance of age in the response of the host (Andervont, 1959; Duran-Reynals, 1953). Duran-Reynals argued with conviction that the administration of Rous sarcoma virus to chick embryos produced hemorrhagic lesions in blood vessels, those lesions containing abundant virus. With advancing age, he argued, chicks become more resistant to the virus, which instead of provoking lesions induces proliferation and malignancy. Likewise young animals respond to small amounts of virus by developing fast-growing tumors, with a tendency toward metastasis. Older, "more resistant" animals require more virus to evoke a tumor that does not metastasize readily. Duran-Reynals considered also that the age of the host is of prime importance in the adaptation of the virus to other species.

There can be little doubt of the correctness of two aspects of these arguments. It is clear that the resistance of the host does influence the rate of tumor growth and spread; and the evidence to be discussed that pertains to actively acquired tolerance bears out Duran-Reynals' own studies of inter-species infection, which are too well known to require summarization (reviewed, Andervont, 1959). Yet it is difficult to conceive that the difference between the production of hemorrhagic lesions in the younger embryo as compared with tumors at day 10 can be related to increasing resistance without evoking a "special class" of resistance to tumors. We have no evidence of the operation of immune mechanisms, either cell-mediated or humoral, at this period of development. One must seek other sources of variation in the host to account for this progressive change.

An unusually interesting attempt to ascertain the effect of age on susceptibility to viruses is Chaproniere's (1957) study of the cultivation of myxoma virus in rat tissues in vitro. Embryonic and newborn rat tissues are more susceptible than older tissues. The changing susceptibility is not linked to known changes in cell population, in permeability to virus (as studied by antibody inhibition tests), to production of inhibitors, or to the lack of factors that can be supplied by embryo extracts. It is especially curious that the loss of susceptibility with age does not apply to two tissues of the reproductive system, gonad and uterus.

We may ask whether in addition to seeking host cell variations, we should expect virus variations as a consequence of host-virus interactions. Andervont (1959) has pointed out that variation is a common trait in viruses and that it would be surprising if the Rous virus had not

shown variations in activity. In a follow-up to earlier studies by Vasquez-Lopez (1936), and Duran-Reynals (1949–50), Groupé, Rauscher, Levine and Bryan (1955–1956) described the growth of the Rous virus in the chick brain. The virus is easily propagated there, producing high titers. Whether this finding is a consequence of the relative absence of homograft immunity mechanisms often attributed to the brain or to another type of host-virus variation is not known.

Duran-Reynals (1953) obtained evidence of virus variation in heterologous hosts. When the Rous virus was administered to day-old ducklings, they developed two types of lesions. One which arose rapidly (30 days or less) could not be propagated in ducks, but produced typical Rous sarcoma in chickens. The other, which appeared later, lost its ability to grow in chickens, but produced a different type of tumor in the duck. It is more likely this is an example of selection rather than host controlled viral variation.

Perhaps the most striking variation of a virus as a consequence of interaction with host cells is that reported by Rose and Rose (1952). Amphibian renal and fat body tumor agents were grown in tissues other than those for which they have a natural predilection. While in some cases they retain their affinity for the original tissue, they may acquire from the new environment a new specific affinity; for example the renal tumor agent acquired an affinity for cartilage; in fact, it may be said that the affinity was not for cartilage in the generic sense but for cartilage of a specific location—digit, or elbow, etc. For a consideration of the influence of host cells on virus specificity in viruses other than tumor viruses, see Hoskins (1959).

For some viruses there is evidence that the younger the embryo the less specific is the tissue tropism shown by an infecting virus. For example, Kung (1948) demonstrated that all of the tissues of the 4-day-old chick embryo are susceptible to influenza A virus, in contrast to the specific tissue susceptibility (respiratory epithelium) shown by Burnet (1940) for the 12- to 15-day embryo. Several other studies indicate that viruses produce a generalized infection in embryos rather than the specific tropism characteristic of the post-embryonic host, e.g., the studies of Bang (1943) with equine encephalitis in chick embryos, Smithburn (1946) with Semliki forest virus, and Taylor (1952) on several African and South American viruses, both also in the chick embryo.

Viruses and Congenital Malformations

In his searching review of experimental studies on congenital malformations, Wilson (1959) relates that there are two infectious agents clearly known to be teratogenic in man: one is the virus, rubella, the other is toxoplasma, a protozoan which appears to invade the central nervous system. Only two cases exist where experimental work with viral induced congenital malformations has been carried out extensively, influenza A and Newcastle disease virus infection of the chick. Wilson cites also the experimental production of malformations in fetal pigs by attenuated hog cholera virus (Kitchell, Sautter, and Young, 1953; Sautter, Young, Luedke, et al., 1953; Young, Kitchell, Luedke, et al., 1955). Other examples are given by Rhodes (1960).

There can be no doubt that Gregg's (1941) demonstration of the incidence of congenital malformations in children whose mothers had contracted rubella during the early months of pregnancy played an important role in focusing attention on virus infections as causes of congenital defects. The initial observations have been confirmed repeatedly (Beswick, Warner, and Warkany, 1949; Caruthers, 1945; Gregg, Beavis, Heseltine, et al., 1945; Swan, 1944; Swan, Tostevin, Moore, et al., 1943), and the nature of the abnormalities produced have been examined in relation to the stage of gestation at which the infection occurred. Dekaban, O'Rourke, and Cornman (1958) have analyzed the data from studies of 108 patients with evidence of damage from maternal rubella. The highest incidence of the three most important anomalies (cataracts, congenital heart disease, and deafness) occurs when rubella is contracted during the first five weeks of gestation, with the incidence declining rapidly subsequent to the sixth week. It has not been possible to devise a model for laboratory study, because the virus is not pathogenic for small animals, chick embryos, or tissue cultures. To complicate matters even more, there is no simple laboratory diagnostic test for the rubella virus or its antibody. The mode of action of rubella virus has not been explained satisfactorily (Rhodes, 1960). The observations do justify the conclusion that infection of the mother early in pregnancy results in develop-

mental abnormalities and that the manifestations in the early embryo differ from those in the adult; the latter conclusion is applicable also to the findings of Hamburger and Habel (1947) who inoculated the 48-hour chick embryo with influenza A and mumps viruses. No specific abnormalities resulted from the inoculation of mumps virus; but influenza A evoked a characteristic syndrome—microcephaly, micrencephaly, retardation of amnion growth, and twisting of the axis. But when the inoculations were made at 96 hours, no specific anomalies were produced by either virus.

Blattner and his associates (1951, 1955, 1953) have studied in detail the abnormalities occurring in chick embryos 22 to 24 hours after inoculation of Newcastle disease virus at 36, 48, 60, 72, and 84 hours of incubation. They report a high incidence of characteristic defects in the neural tube, lens primordia, auditory primordia, visceral arches, limb buds, and olfactory primordia. For each age group there is a different but typical complex of defects. Susceptibility to the virus is greater in the younger than in the older embryos as evidenced by the highest incidence of lethality in the youngest embryos and the decreasing extent of the defect in most organs in each succeeding age group.

Pending a systematic study and comparison of the effects of inoculation of a given virus into the embryo at successive intervals during ontogeny under uniform conditions of dosage and other controllable conditions, any conclusions drawn from the fragmentary evidence available must be tentative. It may be noted first that apart from a large body of negative findings, largely indirect, there are but three carefully delineated demonstrations of the effects of viruses on "early" embryos—human, less than five weeks gestation (rubella) and chick, 36 and 48 hours (Newcastle disease virus and influenza A). It should be noted that in the chick embryo by 36 hours the embryonic axis is laid down and several of the major primordia have been outlined. The implications of these studies, however, are important; without exception they have been interpreted on the basis of the concept of the critical or susceptible period in teratogenesis (see Wilson, 1959, for a review of this concept). For example, Robertson et al. (1955) point out that, in the case of their experiments with Newcastle disease virus, since the route of inoculation is over the blastoderm, it might be expected that surface ectodermal structures would be involved first. Anderson (1940) found with herpes simplex that the site of primary infection depends on the route of inoculation. It may be pointed out, parenthetically, that McKenzie and Ebert (1960) observed that the effects of the metabolic inhibitor antimycin A on the early chick embryo in vitro depend also on the surface to which it is applied. Robertson et al. (1955) also point out that, according to Gottschalk (1954), the Newcastle disease virus along with certain others appears to be restricted in its propagation to cells lining a surface in contact with their environment. This conclusion is in line with their own finding that the neural tube, lens vesicle, and auditory vesicle, all of which are affected by the virus, are involved when they are exposed to the exterior at the time of inoculation.

Robertson et al. (1955) stress that "an important critical factor in determining susceptibility to the virus at this embryonic stage is the amount of proliferation and differentiation occurring within the organ at the time of exposure" and argue that the virus finds a highly suitable environment for proliferation in areas of high metabolic activity. They state that it is generally agreed that overall metabolism is at its highest level in the early embryos and gradually declines with age, but regrettably they do not document their statement. Their findings are clear-cut, but the interpretation, based on an uncertain higher metabolic rate providing better ground for virus proliferation, does not appear to be justified. The necessity of a high host cell metabolic rate to support viral growth has not been clearly demonstrated. In fact, it must be emphasized that proliferation of this virus in the early embryo has not been demonstrated. Robertson et al. (1955) are aware of this fact and suggest an alternative explanation, based also on the concept of susceptible periods, but requiring not the proliferation of virus but the "toxicity" of the virus (cf. Davenport, 1952; Ginsberg, 1951; Rake and Jones, 1944; Smadel, Rights, and Jackson, 1946).

From this discussion several critical questions emerge: (1) At what stage in their development can embryonic cells be *infected by a given virus*? When will embryonic cells support proliferation of the virus? (2) Are the well documented examples of malformation produced by "virus" actually the consequence of viral infection and proliferation or do they result from "toxic" ef-

fects otherwise not defined? (3) Is it possible that cells of the early embryo may be "infected," but that the virus remains in a latent stage until the maturation of conditions favoring proliferation? (4) To what extent must we consider latent viruses, including viruses without distinctive pathogenic action in the adult animal, as causative agents in teratogenesis?

We can scarcely begin to answer these questions. The ability of the 1-day-old chick embryo to support viral growth is the subject of a recent report by Matumoto, Saburi, and Nishi (1959). These investigators state that they have been able to cultivate the Rift valley fever virus (both neurotropic and pantropic strains) in the 1-day embryo. It must be noted, however, that the virus was inoculated into the yolk, some 5 to 10 mm. from the blastoderm. Moreover, in harvesting the virus the entire contents of the egg were homogenized. Thus although it is said that the pantropic virus begins to increase within 24 hours after inoculation, reaching a maximum at 48 hours, and that the neurotropic strain reaches a maximum at 2 to 3 days, it cannot be said whether the virus has proliferated in the embryo or in the extra-embryonic regions. Matumoto et al. (1959) refer to the successful cultivation of several other viruses by the same technique, including dengue, distemper, Japanese encephalitis, vaccinia, and variola. Yoshino and Taniguchi (1956a, 1957) have reported the proliferation of herpes simplex in the 1-day-old chick embryo.

Let us go on to raise still another set of problems. The one virus that has been studied over a period of several days during development is influenza A. We have remarked on the specific syndrome produced in the embryo by inoculation at 48 hours, and the absence of such a syndrome at 96 hours. Kung (1948) states that all tissues of 4-day embryos are susceptible to the virus. This difference in syndrome may reflect a loss of specificity; on the other hand, the initial effects may not be those of the virus in the usual sense. Then as development proceeds, older embryos (12 to 15 days) show specific tissue susceptibility—in the respiratory epithelium (Burnet, 1940). The pattern, then, is apparent specificity (possibly misleading), generalized infection, specific infection. Again we may ask several questions: (1) To what extent is this pattern characteristic of other viruses; (2) What is the meaning of the tissue specificity at 12 to 15 days? To put it another way, if the several tissues of the embryo were cultured separately in the presence of the virus would they be susceptible? Is there a loss of ability to accept and support the virus in all tissues but the "specific" ones? Or does the specificity reflect a competitive situation, in the sense that as the one tissue matures it acquires a property making it more favorable to the virus?

In attacking these problems the initial approach need not be highly sophisticated. In fact what are needed most are detailed descriptive studies of the ability of viruses to infect embryos —of several species—at progressive stages in development. Carefully controlled experiments are required in which a given virus is examined critically during ontogenesis. When does it infect the embryo proper? When does it infect the membranes? Is there a period during which congenital malformations are produced? If so, is infectivity required? Does the syndrome of effects initially suggest pantropism followed by increased cell specificity as development proceeds? Although information on any of the viruses would be useful, certain of them may present better experimental possibilities than others. It is believed that viruses that show unusual degrees of specificity in newborn and adult animals will be favorable targets. As examples we may cite the Coxsackie viruses: Coxsackie A being myotropic (Sacerdote de Lustig, 1954; Shaw, 1952) and Coxsackie B neurotropic (Levaditi and Henry-Eveno, 1952a; Levaditi, Vaisman, and Henry-Eveno, 1952b).

It will be especially useful to know for each virus the extent to which specificity requires the intact organism. Do viruses tend toward pantropism when studied in vitro? It is interesting to note that Wolff and Goube de Laforest (1959) have shown that avian variola virus produces a cytopathology in skin organ cultures comparable to that found in vitro, but cytopathology in tissue culture is much different from this normal picture. This question is directed toward an elucidation of virus-host relations at two levels: first, the development of host defense mechanisms, and second the nature of virus receptors. The first of these topics will be the subject of the concluding chapter; we can comment on the second only briefly. Gottschalk (1959) has presented a penetrating review of the chemistry of virus receptors. He points out that for many animal viruses it seems to be characteristic that

their host cells are endowed with phagocytic powers, citing the epithelial cells of the respiratory and alimentary mucous membranes, the alveolar cells of the lung, the vascular endothelial cells, and the endothelial Kupffer cells. Here the intake of the virus is termed "viropexis." He believes that viruses with a wide range of host cells (vaccinia, ectromelia, psittacosis) rely on random collisions with host phagocytes. For these viruses, then, one would expect the pattern of their effects on embryos to follow the formation of phagocytic cells. Animal viruses with a restricted range of host cells, of course, have developed a specific mechanism of attachment as preliminary to the intake of virus. Such cellular receptors have been described for influenza, Newcastle disease, mumps, and fowl plague viruses; and their chemistry has been elucidated in part. It appears, for example, that the influenza virus cellular receptors are built up like the soluble influenza virus hemagglutinin inhibitors, that is they are conjugated proteins with oligosaccharide prosthetic groups. The size of the oligosaccharide may vary with the type of mucoprotein. The oligosaccharides have as terminal units acetylated neuraminic acid residues, joined to an adjacent sugar residue through a neuraminidase-susceptible glycosidic linkage. Perhaps it is not too early to inquire whether these receptors are present in undifferentiated cells—and to examine the relationship of their formation to the acquisition of other specific properties of cell surfaces.

INTERCELLULAR TRANSFER OF GENETIC AND EPIGENETIC POTENTIALITIES

The virus is not only an agent for modifying the course of development, and for detecting when differences arise in cells; cell specialization must arise from differences in the genetic and epigenetic depots of the cell. In this chapter we propose to discuss experiments from several disciplines which focus on one common point, namely recombination between vertebrate somatic cells in relation to differentiation and growth. What has this to do with viruses and embryos? Our point of departure is the dramatic phenomenon of virus transduction in bacteria, which has focused attention on the possibilities of recombination between vertebrate somatic cells. Can animal viruses be used to carry out genetic operations with embryonic cells? Do methods and concepts of virological and bacterial genetics suggest new and fruitful approaches to the problem of genetic-epigenetic relationships during development? Can intercellular transfer of subcellular units and/or viruses modify patterns of synthesis in embryonic cells? We shall briefly review several areas germane to these questions: first, the transfer of enzyme forming capacity by epigenetic recombination in bacterial and vertebrate cells; second, the transfer of antibody forming capacity in vertebrates; and third, the selective uptake and intercellular exchange of subcellular particles in the chick embryo; and last, a discussion of some experiments leading up to and resulting in the use of viruses to facilitate transfer of information between embryonic cells.

Epigenetic Recombinations

One approach having particular relevance to our considerations is the phenomenon of epigenetic recombination. Epigenetic recombination is defined arbitrarily as nongenetic recombination; the recombination process consists of the transfer of information between donor and receptor cells. The transferred elements have a transient existence, for they do not possess the fundamental genetic property of regular autoreplication (hence, *epigenetic*); and yet the effect on the host phenotype may be profound and long lasting.

In 1955, Reiner and Goodman reported that during induction of gluconokinase in *E. coli* the rate of formation of the enzyme could be increased considerably by an extract prepared from cells which already contained gluconokinase. This cell-free extract also could elicit enzyme formation in noninduced cells in the absence of inducer. The extract, devoid of enzymatic activity itself, was RNA prepared by ethanol precipitation and deproteinization by the Sevag technique. After RNAase digestion the activity remained and was dialyzable; it could be replaced partially by yeast nucleic acid or pyrimidine nucleotides. The fact that the active extract was not completely specific, that the extraction had to be carried out in the presence of gluconate, and absence of subsequent confirmation all point out the need for further exploration of this phenomenon.

Hunter and Butler (1956) have reported similar results with the inducible β-galactosidase of

Bacillus megaterium. Addition of RNA extracted from cells grown on lactose to cells growing exponentially on glucose stimulated enzyme formation by a factor of 2.5 over control levels; the nucleic acid had no inherent enzyme activity. However, these workers pointed out that the experiment was difficult to reproduce, and the specificity of the phenomenon was not examined in detail. It is interesting to note that stimulation was obtained in the presence of glucose, a potent inhibitor of β-galactosidase induction in *E. coli*, which is effective because of its presumed action on the inducer transport enzyme, permease.

The recent findings of Kramer and Straub (1956) also are of interest. The system examined was the inducible penicillinase of *Bacillus cereus*. A heated 1 M NaCl extract of a strain containing constitutive enzyme specifically induced a transient (20 minutes) and rapid penicillinase formation in cells of inducible strain in the absence of inducer. In order to demonstrate activity the receptor cells had to be pretreated with ribonuclease and subsequently washed; ribonuclease treatment of the extract, which had no inherent enzyme activity, abolished the effect. However one might suppose, especially since there was no deproteinization, that there is a reactivation of denatured enzyme in the receptor cells. Unfortunately, this phenomenon, although apparently real enough, has been extremely difficult to reproduce (Pollock, personal communication).

All of these reports are preliminary, but it is held likely that proper conditions for demonstrating introduction of enzyme-forming machinery into cells will be found. One of the more important aspects of the problem is the question of the autoreplication of such synthetic units (cf. Waddington, 1956). Are they really extranuclear genetic elements? The experiments reported by LeClerc (1954) exemplify one approach to the problem. In five out of six experiments inoculation of the chick chorioallantoic membrane with microsomes of embryonic liver led to a two to six-fold increase (after 24 hours) in glucose-6-phosphatase, a specific microsomal enzyme. Although microsomal duplication is one possible interpretation, enzyme reactivation, unmasking of latent enzyme (cf. lysosomes, De Duve, 1959), or even epigenetic recombination may be taking place. Likewise, other reports of the stimulation of cell activity by RNA, such as increased basophilia (Shaver and Brachet, 1945; Shaw and Shaver, 1953), may be interpreted in similar ways; or more simply, the RNA may be producing a high concentration of purines and pyrimidines which stimulate cellular activity. The specificity of such phenomena must be examined with care, and this goal unfortunately has not always been achieved. Clearly, the phenomenon of epigenetic recombination must be kept in mind when examining the effects of extracts on embryonic cells. A diffusible inductor need be no more than a transfer of a specific enzyme-forming system which acts at a crucial step in the epigenetic history of the cell (Delbruck, 1949; Hinshelwood, 1952, 1953).

Recombination Experiments with Particulates

The role of microsomal particles in protein synthesis has been treated fully in a number of reviews (e.g. Roberts, 1958); until recently, however, clear-cut evidence of net synthesis of specific protein was lacking. Webster (1959) lists at least four species of microorganisms in which net synthesis of a small amount of protein (as contrasted with simple amino acid incorporation) has been achieved in crude preparations: *Staphylococcus aureus*, *Bacillus megaterium*, *Alicaligenes faecalis*, and *Tetrahymena pyriformis*. What appear to be the most conclusive experiments, however, are those of Webster himself (1959) who has demonstrated the synthesis of "soluble" protein by ribonucleoprotein particles isolated from peas. When these particles, which have one major component in the ultracentrifuge, are incubated with a mixture of amino acids, energy sources and a polynucleotide fraction, the soluble protein in the medium increases appreciably. The "cytoplasmic" polynucleotide is required for net synthesis. The "soluble" protein is composed of several components (two major, three minor) and has enzymatic activity in hydrolyzing adenosine triphosphate. Of uncommon interest are the results of experiments employing fluorodinitrobenzene for analysis of N-terminal amino acids. When the particles are incubated with a single labeled amino acid the label is recovered always in the N-terminal position, yet when the labeled amino acid is presented along with a mixture of unlabeled amino acids the label is recovered largely in non-N-terminal positions. Webster suggests a likely explanation: protein synthesis proceeds by sequential addition of car-

boxyl-activated amino acids; when a single amino acid is added, all the reactive sites become filled rapidly and synthesis stops, whereas the mixture permits continuation of the process.

None of the studies employing particles from animal tissues are as satisfactory. Evidence stemming from studies of albumin synthesis are reviewed by Ebert (1958b). Schweet, Lamfrom, and Allen (1958) have described the synthesis of soluble protein, mainly hemoglobin, in a system containing microsomal particles from rabbit reticulocytes plus soluble enzymes. Kern, Helmreich, and Eisen (1959) have shown the presence of antibody activity on particles with the sedimentation characteristics of microsomes. The activity was induced in lymph nodes which drain sites of injection of 2,4-dinitrophenylbovine gamma globulin into guinea pigs, and was specific for the DNP group. The presence of antibody cannot be taken as proof of its synthesis on the microsomes, the finding being equally consistent with the synthesis of antibodies elsewhere and their translocation to microsomes.

Serum Antibody and Gamma-Globulin in Chicks and Baby Rabbits After Transfer of Nucleoprotein from Mature Animals

Intriguing questions are posed by recent attempts to transfer antibody-forming capacity to unimmunized animals with extracts from cells of immunized animals. Sterzl and Hrubesova (1957) immunized adult rabbits with *Salmonella paratyphus* B and removed the spleens 24 to 48 hours after injection. After homogenization and differential centrifugation, ribonucleoprotein was extracted with 0.14 M NaCl and purified by ethanol precipitation; DNA-protein was extracted from nuclei with 1 M NaCl. Then 80 to 700 μg. of the ribonucleoprotein or 110 to 300 μg. of the deoxyribonucleoprotein was injected into 5-day-old rabbits, which normally do not respond to the antigen. Controls received extracts from unimmunized animals. No antibody was detected in the nucleoprotein itself. The most interesting result is that extracts of spleens recovered 48 hours after immunization evoked antibody titers of 1/16 to 1/32 in 5-day-old rabbits 5 to 10 days after injection. These titers are so low that their significance is difficult to assess. Hrubesova, Askonas, and Humphrey (1959) have repeated these experiments with ribonucleoprotein in the same system, finding that in two out of three experiments, the titer, although low, was higher than in the controls. They also injected C^{14} amino acids on the second and eighth days after the injection of nucleoprotein into the young rabbits. No difference in C^{14} incorporation to *Salmonella* absorbable protein was apparent, but they point out that nonspecific absorption easily could obscure any striking effects. No performed antibody could be detected in donor extracts, but titers of 1/8 to 1/10 were found in donor serum 48 hours after injection. If the blood of young rabbits was collected 9 days after ribonucleoprotein injection the incorporation of C^{14} activity into gamma globulin was greater in experimental than in control rabbits; radioactivity of alpha and beta globulins did not differ from controls.

Van Doorenmaalen (in Ebert, 1959b) attempted to determine whether the findings of Sterzl and Hrubesova are of general significance, applicable to other antigens and other species. Crystalline bovine serum albumin (BSA) was selected as the antigen, and chickens were the recipients. The findings have been negative. Three principal types of experiments were conducted, all of them having one feature in common, viz. the DNA-proteins and RNA-proteins employed were extracted, following the procedures described by Sterzl and Hrubesova, from the spleens and bursae of Fabricius of adult chickens immunized 2 days previously. Nine-day-old chick embryos of the White Leghorn strain were injected intravenously with BSA to evoke tolerance for that antigen. Twenty-two tolerant chicks (16 to 31 days post-hatching) were injected with four separate preparations of spleen DNA-proteins and RNA-proteins. Antibodies could not be detected following the injections. Thinking that the condition of tolerance, a variable not present in the experiments of Sterzl and Hrubesova, might interfere with antibody formation, a number of juvenile chickens were injected with seven separate preparations of spleen DNA-proteins and RNA-proteins. Again no antibodies were detected. In the chicken the bursa of Fabricius appears to play an important role in antibody formation. Thus it was chosen as an additional source of nucleoprotein. Juvenile chickens were injected with bursa RNA-proteins; others were inoculated with bursa plus spleen RNA-proteins. Antibodies were not detected. In view of the many variables in experiments of this type, the preliminary nature of the work must be

reiterated; nevertheless antibodies have been detected in *none* of 48 animals studied employing a highly effective antigen-precipitin system. It must be emphasized, also, that by precipitin techniques, van Doorenmaalen could not demonstrate the occurrence of antibodies against the injected nucleoproteins; the question arises, therefore, whether the nucleoproteins may be destroyed rapidly by serum nucleases.

The findings of Jankovic, Isakovic, and Horvat (1959) are in agreement with those of van Doorenmaalen. Jankovic et al. injected human gamma globulin into adult chickens; by the Coomb's technique, antibodies with titers of 1/1000 to 1/3000 were detected. After 3 days, the spleens of the adult chickens were removed and a ribonucleoprotein fraction was extracted. It contained neither detectable antibody nor antigen. This ribonucleoprotein was injected into two groups of young chicks (5 and 12 days post hatching, respectively). When these chicks were bled at 1, 3, 6, and 10 days after the injection, no antibodies were induced against the nucleoprotein. Jankovic et al. state that they were able to demonstrate the presence of RNA-ase in the serum of adults and young chicks.

What are we to conclude from the failure to extend the findings of Sterzl and Hrubesova et al.? Were the statements of Hrubesova et al., based only on the observation that anti-*Salmonella* antibodies can be detected in the recipients, one would be inclined to conclude (especially in light of the finding of Kern et al., of antibody in ribonucleoprotein granules) that *antibody* was in fact transferred with the ribonucleoprotein. Yet the finding of splenomegaly in the recipients, coupled with an increase in gamma globulin, does argue that synthesis has been initiated in the host. In this respect the findings are in agreement with those of Ebert and DeLanney (1960) who have reported that the inoculation of homologous spleen microsomes into the chick embryo stimulates the growth of the host's spleen.

Selective Uptake of Subcellular Fractions by the Chick Embryo; Modification of Patterns of Synthesis in the Host

In considering the modification of patterns of synthesis in embryonic tissue, we take up next the effects of transplanting adult tissues, notably spleen and other immunologically competent tissues, to the chick embryo and its membranes (DeLanney, 1958; DeLanney and Ebert, 1959a, b; Ebert, 1951, 1954, 1955, 1957, 1958a and b; 1959a, b, and c; reviewed Billingham, 1959; Ebert and DeLanney, 1960). Many of the results can be explained best by an immunological reaction of the graft against the host. However, other experiments demonstrate that the reaction is not this simple; a host versus graft reaction is involved, and perhaps there is also a specific localization of subcellular material and ensuing growth stimulation apart from an antigenic stimulation of cell proliferation.

A summary of the cytological effects of spleen grafts will provide a suitable background for the discussion. DeLanney and Ebert (1959a and b; Ebert and DeLanney, 1960) have followed the cytological changes in the chorioallantoic membrane and host spleen at closely timed intervals after implantation of homologous adult spleen to the membranes of 7- or 9-day-old chick embryos. Immediately after implantation the epithelium of contact thickens; the mesenchyme forms spindle cells and undergoes a shift toward myelogenesis. Even though the graft is not fully incorporated in 24 hours, regional differences appear in it: the perimeter contains many large basophilic mesenchyme cells with large distinct nuclei, and the central mass contains dense aggregates of small cells. In the zone of contact the chorionic epithelium is eroded, clusters of granulocytes appear, numerous spindle cells gather at the border, and tongues of small cells with dense nuclei invade the membrane; although the latter are few in number, the evidence suggests they originate in the graft.

The same processes continue into the second day. Consequently, the chorioallantois around the graft differs strikingly from normal membrane, for it is thickened by cell aggregates which are concentrated under the graft; also masses of small lymphocytes encircled by spindle cells, and occasional granulocytes are present. Pronounced accumulations of granulocytes by day 11 (after implantation at day 7) indicates a shift to myelogenesis; hemocytoblasts are present, mucopolysaccharide content increases, and cysts (possibly of graft origin) are surrounded by giant cells.

The host spleen concomitantly undergoes a dramatic shift to myelogenesis, a large weight increase being evident by day 12 (after grafting at day 7). Subsequently the reaction becomes intense, granulopoiesis reaches a peak, muco-

polysaccharide increases, and finally vascular breakdown, necrosis and fibrosis ensue.

Let us review briefly the evidence for the first hypothesis. There is a considerable body of evidence to support the thesis that the effects of the spleen graft on the host spleen are mediated by an immune reaction. First, the reaction is quantitatively organ specific and class specific, but not species specific. Of 11 donor tissues studied by Ebert, only spleen > thymus > liver (in that order) were effective, but Van Alten and Fennell (1959) and Billingham and Silvers (1959) respectively have shown that grafts of small intestine and skin also affect the host spleen. Each of these organs contain immunologically competent cells; hence, it appears consistent to state that the reaction is tissue-specific with the added stricture that it may be possible to define it more precisely as cell specific. Perhaps the quantitative organ specificity reflects the proportion of immunologically competent cells a tissue contains. Spleen of other avian species (duck, Ebert and DeLanney, 1960; turkey and pheasant, Mun, Kosin, and Sato, 1959) produces some effect on the host spleen, but never as much as homologous spleen. Mouse spleen (Ebert and DeLanney, 1960) and guinea pig spleen (Mun, et al., 1959) are completely ineffective.

Second, x-irradiation of adult chicken spleen removes its ability to affect the homologous organ of the embryo. According to Mun, Kosin, and Sato (1959) after irradiation at 205 r to 810 r, splenic grafts retain their effectiveness. At higher doses, between 1230 r and 1640 r, a significant decrease in effectiveness is observed; and at doses above 1845 r, all activity is lost. Kryukova (1959b) showed that while non-irradiated homologous spleen cells and cells x-irradiated at 300 r caused approximately sixfold enlargement of the embryo spleen, cells irradiated with 900 r and 1200 r had little or no effect.

Third, recent work using spleens from inbred lines (1959) demonstrates that inter-strain grafts produce a larger effect than intra-strain grafts, a finding expected if the reaction were an immunological one. Adult spleen grafts from donors of the S line (selected for leukosis susceptibility) affected spleens in embryos of the same line to a lesser extent than in embryos of the R line (selected for leukosis resistance); the converse experiment produced the same results, although the effect of R spleen on S hosts was not as marked. S line donor spleens implanted to F_1 (R × S) hosts produced an effect similar to inter-line S into R grafts, but R donor spleens to the F_1 produced an effect comparable to the intra-line combination. These findings agree essentially with those of Cock and Simonsen (1958) who also used inbred White Leghorn lines. In the latter study, when blood from adult birds of line I was injected into newly hatched F_1 chicks (C × I), the host livers and spleens were affected drastically; but when F_1 blood was injected into F_1 chicks, only a slight effect was observed.

Fourth, the reaction can be transferred serially by intracoelomic and chorioallantoic transplantation of embryonic host spleen following a primary graft of adult chicken spleen. For example, Ebert found that grafts made to the coelom of the host chick embryo before the appearance of the host spleen, stimulate the host's spleen by the tenth day. The question was raised whether such a stimulated 10-day embryonic spleen, (normally not an effective donor) might be a competent donor. Grafts were made to a number of 4-day embryos, which were permitted to develop until the tenth day when the host spleens were harvested and used as donors for the second set graft, the experiment being carried through four passages. The growth promoting activity was not diluted by serial passage, but was maintained relatively constant. DeLanney and Ebert (1959a; Ebert and DeLanney, 1960) have reported also the serial transfer of the reaction through three transplant generations by fragments of chorioallantoic membrane previously in contact with a primary adult graft. The second set (or third set) transplantation to the membrane of 7- to 9-day-old embryos of fragments of chorioallantois taken from reactive sites surrounding the original first set spleen implant results in intensified reactions in second and third generations characterized by extreme conditions of vascular breakdown. These grafts produced a rapid destruction of the surrounding membrane which became moribund in four days, containing widespread pycnosis and nuclear breakdown and aggregates of giant cells.

Simonsen (1957) demonstrated a comparable deleterious effect on the host spleen by intravenous injection of juvenile or adult chick leucocytes or spleen cells to the 18-day-old chick embryo, a reaction which he serially transferred without dilution for nine generations. Accord-

ing to Simonsen, the recipients have to be of an age in which tolerance of homologous cells can be induced; the donors must be old enough for an immune response.

Moreover, serial transfer experiments argue for the transfer of viable cells. Perhaps as Simonsen has argued, the increase in size of the host spleen is due solely to the proliferation of adult donor cells populating the embryonic spleen, the proliferation being the result of antigenic stimulus. Alternatively, the reaction may be primarily a host reaction, the stimulus issuing from the graft evoking an abortive or incomplete reaction on the part of the host. Although the chick embryo appears to be incapable of a complete immune response, preliminary evidence has been advanced (Ebert and DeLanney, 1960) suggesting that it is capable of recognizing an antigenic stimulus. Coupled with other evidence to be cited shortly, this finding has led DeLanney and Ebert to postulate that in response to the stimulus of the graft, the host spleen proliferates rapidly, and in the absence of fully differentiated regulatory mechanisms that proliferation may proceed wildly, resulting in the pathologic effects described in the foregoing pages.

Studies using radioactively-labelled transplants, while not decisive, have revealed a predominant localization of material in the homologous organ, but preclude a massive transfer of cells. Perhaps a clarification of the role of donor and host cells may come from studies now in progress that use cytological and radioactive markers. Biggs and Payne (1959) have presented significant preliminary findings in a study in which they identify proliferating donor cells in chick embryos injected with adult chicken blood. In the chicken the fifth largest chromosome is paired in the male, single in the female. Cockerel blood is injected into 14-day-old embryos which are sacrificed at day 18, demecolcine being administered 3 hours before sacrifice. In enlarged spleens taken from female embryos, male chromosomes can be identified, proving the localization and proliferation of some donor cells. The relatively high number of dividing female cells, however, suggests to Biggs and Payne that an appreciable component of the splenic enlargement is provided by host embryo cells. The authors believe that it is likely that the evidence will prove neither point of view entirely correct—that the reaction is not an all-or-none reaction on the part of either graft or host cells; rather the spleen and other immunologically competent tissues serve as the principal "battlegrounds" in a competition between donor and host cells, and that depending on several factors, the outcome may be in either direction.

These four lines of evidence strongly suggest an immunological basis for stimulation of host embryonic spleen by an adult spleen graft. Even the findings concerning species specificity, which stand in apparent contradiction, possibly can be dismissed on the basis of failure of graft cells to persist in the foreign environment long enough, or in healthy enough condition, to act immunologically. But, as Simonsen and Jensen (1959) have reported, some experiments forcefully suggest that there are cases when immunologically active donor cells are not necessary for homologous stimulation. The evidence stems from an analysis of splenomegaly in transplantation chimeras, in some of which donor cells could not be detected, while in yet others donor cells appear to have lost, or never acquired, reactivity against the recipient. Simonsen and Jensen state that it is probable that both graft versus host and host versus graft reactions can lead to "secondary disease."

Do subcellular particles affect the homologous host embryonic organ? Experiments of Andres (1955) have shown that frozen, thawed, triturated tissues may even be more effective and specific than live tissues. Ebert (1954, 1955, 1958b) has shown that homogenates of previously frozen S-35 labelled adult kidney or spleen injected into the 9- or 10-day-old chick embryo showed a differential incorporation in the host organ after 24 hours. The differential was not of the same order as that obtained with living transplants, but was reproducible and real. A standard fractionation of the homogenate by differential centrifugation in sucrose solutions revealed the activity was confined to the microsomal and supernatant fractions, was non-dialyzable, heat labile, and destroyed by ashing. The small quantities of subcellular fractions tolerated by the embryo did not produce significant growth stimulation.

Van Haeften (1958) placed cell free homogenates of adult chicken spleen, thymus, and skeletal muscle on the chorioallantois of 9-day-old chick embryos. He observed that the spleen homogenate produced a myeloid reaction on

the stroma of the membrane, hypertrophy of the histologically normal host spleen, and a general increase of circulating blood cell types. Thymus homogenate produced lymphocytosis and eosinophilia. Moreover, Croisille (1958) deposited cell-free extracts of spleen and liver on the vascular area of the chick embryo at days 3, 4 and 5, the embryos being recovered at days 12 through 18. Only 17-day-old chick embryo liver consistently produced a statistically significant growth stimulation of the homologous host organ; but Croisille found that both adult spleen and liver extracts produced a slight stimulation of the homologous organ (and also general growth stimulation), which in some series was quite dramatic. Unfortunately, no histological examination of the stimulated organs was made. The effect could not be produced in organs cultured in vitro. Ebert obtained an increase in host spleen weight by adult grafts encased in millipore filters before being implanted in the chorioallantois, finding the same order of stimulation (30 percent) as did Croisille (in Ebert and DeLanney, 1960).

These findings prompted Ebert and DeLanney (1960) to reexamine the question by injecting subcellular fractions intravenously (the more effective route) or directly onto the membrane. The fractions were prepared by the procedure of Moloney (1956) involving digestion of the spleen by hyaluronidase, protamine sulfate precipitation, trypsin digestion, and differential centrifugation. Intravenous injection of 0.1–0.15 ml. of microsome fraction to 9- to 11-day-old embryos produced a significant increase in the weight of the host spleen compared to sham operated controls or embryos receiving microsomes prepared from other organs.

Should one attempt a synthesis of findings of granulocytopoietic splenomegaly and subsequent host spleen destruction after grafting with the stimulation following administration of cell free extracts? Perhaps the two phenomena are completely different. Or do the graft vs. host and host vs. graft reactions mask another reaction of organ specific growth regulation? In this case the microsome experiments could be interpreted on the basis of the concept of feedback equilibrium, for they suggest a balance between tissues of different physiologic age (Glinos, 1958; Paschkis, 1958; Rose, 1958; Weiss, 1955; Weiss and Kavanau, 1957). Or do the results only signify, as mentioned before, an immune (hypersensitivity) reaction on the part of the host? If so, we must return to the enigmatic question of tissue and subcellular fraction specificity, which might be explained by the more effective exposure of the spleen to antigens. Or could splenic growth represent a phenomenon of epigenetic recombination in which adult particles are carrying on synthesis in an embryonic environment? Since there is no evidence for serial transfer of activity of microsomes, it is premature to argue that they are infective. Despite the recent contributions of Tumanishvili (1958), perhaps it is best at present to consider findings with immunologically competent tissues apart from stimulation by cell free extracts. The best synthesis of the two sorts of phenomena will undoubtedly issue from more critical experiments.

Microsomal Particles and Embryonic Induction

Finally, it is tempting to propose that embryonic induction is in fact epigenetic recombination. Unfortunately, not only complex molecules capable of carrying enough information to shift the epigenetic history of a group of cells are efficacious; but pH changes, urea, and a host of other treatments can shift the fate of embryonic cells. Brachet (1957) has summarized the literature of embryonic induction, emphasizing the evidence implicating RNA and RNA-protein. Despite several decades of intensive research by Brachet himself, Toivonen (1954), and Yamada (1958), to name only a few, the evidence is indirect and inconclusive. Ebert (1959b) has pointed out that one must write "RNA or RNA-protein," for the roles played by the nucleic acid and protein moieties have not been clarified. In fact the questions of passage and localization of RNA, RNA-protein, or other inductive agents are not resolved fully.

One fundamental difficulty is semantic. To expect that induction of the central nervous system by chordamesoderm can be compared to induction of epithelial tubules by metanephrogenic mesenchyme, for instance, is an unwarranted generalization. Until more evidence is at hand, the word induction must always be qualified and defined operationally. The interpretation of experiments on embryonic induction must now be tempered by a consideration of the very important work of Barth and Barth (1959). Presumptive epidermis of *Rana pipiens* gas-

trulae, a material less subject to neuralizing influences than urodele ectoderm (Smith and Schechtman, 1954), will differentiate into a variety of tissues (muscle, nerve, ciliated cells, etc.), in vitro, in a simple balanced salt solution to which serum globulin was added.

One particularly striking report, however, is the observation of Niu (1958) that amphibian gastrula ectoderm cultured in the presence of extract; Niu presented evidence that the active component is RNA, but addition of non-specific protein to the nucleic acid increased the frequency of induction.

In view of the inconclusiveness of the evidence that might enable one to determine whether or not specific protein is essential for the action of RNA (or, indeed, whether any *specific* inductor is involved) and in view of the positive evidence for the involvement of microsomes in protein synthesis, Ebert (1959b) has undertaken experiments to determine whether microsomes of adult tissues can act as homoiogenetic inductors when incorporated into embryonic cells. We are confronted with at least two possibilities which might explain the inconsistencies in earlier findings: (1) failure to prepare a "physiologically active" RNA or RNA-protein; (2) failure of RNA or RNA-protein to enter the cell or to compete effectively with its counterpart in the recipient cell. The experiments of Kramer and Straub (1956), who found in transferring "enzyme-inducing capacity" by RNA that it was necessary first to treat the recipient cells with RNAase, suggested that attention should be paid to measures that might facilitate passage and incorporation of the inductive agent.

The question was raised whether animal viruses might be employed to facilitate the passage of macromolecular or particulate inductive agents. The idea was advanced that a combination of RNA or RNA-protein from a normal tissue with a suitable animal virus might provide a means of transferring the inductive stimulus to another tissue. The virus need only facilitate epigenetic recombination by affecting the receptor cell surface, but at the same time the possibility of incorporation of host cell RNA into the virus and a formal mechanism comparable to transduction cannot be completely discounted.

In the study reported by Ebert (1959c) the passage and incorporation of tissue microsomes has been facilitated by combining them with a virus of the RNA type. The following criteria were established: (1) the site of inoculation should be one in which the tissue to be induced is not differentiated normally, yet it should be labile as revealed by its ability to be channeled into directions it normally does not take. (2) The tissue to be induced should be one that is recognized readily by microscopic techniques yet is also amenable to analysis by biochemical and immunochemical methods. (3) The virus to be employed must be an RNA-virus and must have an affinity for the tissue with which it is combined. The following system was selected: (1) chorioallantoic membrane; (2) cardiac muscle; (3) Rous sarcoma virus.

The methods employed have been outlined elsewhere (Ebert, 1959c); only a brief outline of the principal findings will be given at this time. Rous sarcoma is grown on the chorioallantoic membrane of the chick embryo following established procedures (Keogh, 1938; Prince, 1958a, b, and c; Rubin, 1955), the virus employed being derived from the standard Rous Number 1 chicken sarcoma. Inoculations were made to the chorioallantoic membrane of 11-day-old White Leghorn embryos, tumor masses being harvested at various intervals thereafter, but usually at 5 or 7 days. Freshly harvested tumors were used for the preparation of stock virus suspensions and for the combination experiments.

Equal quantities (by wet weight) of fresh Rous sarcoma and fresh cardiac muscle (adult chickens or 18-day-old chick embryo) were combined and extracted by the procedure of Moloney (1956). Comparable quantities of each tissue alone also were extracted. The "microsomal" preparations resulting from this procedure (heart "microsomes," Rous sarcoma "microsomes," or heart plus Rous sarcoma "microsomes" were inoculated on the chorioallantoic membrane of embryos at 11 days; no growths have resulted from the inoculations of heart microsomes alone. Both Rous sarcoma microsomes and heart plus Rous microsomes produced growths on the membranes, the masses being indistinguishable grossly. Contractions have not been observed. When the masses were studied histologically, differences were observed in the two groups: inoculation with virus alone evoked the characteristic Rous sarcoma; inoculation with the heart plus Rous fraction evoked masses

which contained to a varying degree, intermingled among typical sarcoma cells, muscle or muscle-like elements. The incidence of clearly recognizable cross-striated muscle was low, but there were found among the tumor cells large numbers of cells and fibers which were muscle-like. It is emphasized that the reaction is not "all-or-none," both the quality and quantity of muscle produced varying widely.

Ebert (1959b) has summarized findings based on a study of 586 masses recovered following the inoculation of the combined fraction. Of this number 163 (28 percent) contained muscle-like elements. These findings have been compared with 236 masses following the virus alone in which no muscle elements were observed and 231 inoculations of cardiac microsomes alone in which no masses were formed.

What is the role of the virus? Is it modifying the permeability of the cell, permitting passage of the "normal" microsomal agent? Is it in some manner diverting or inhibiting the host's RNAase, preventing destruction of the tissue microsomes in the inoculum? Or is there an epigenetic transfer involving information stored in RNA? Speculation concerning transduction-like mechanisms is unwarranted at this time. A conclusion is clearly impossible, pending further information but the following additional facts may be of interest.

The normal tissue and sarcoma must be coupled at the outset of the experiment carrying them through the extraction procedures together. Results with combinations of the virus and microsomes carried through the extraction procedures separately and mixed immediately before inoculation have been almost entirely negative, although in two experimental series a few "muscle-like" elements were observed. In this connection attention centers in the first step of the extraction procedure, which would appear to provide opportunity for intracellular recombination. In this step, a 6.6 percent suspension of heart plus sarcoma in 0.15 M potassium citrate containing 1 mg. of hyaluronidase per 100 ml. is allowed to digest for 1 hour at room temperature. During that hour, the suspension is mixed for 30 seconds every 10 minutes in the Waring Blendor, the final mixing being followed by centrifugation at 2500 g for 20 minutes.

In the initial experiments the conditions favored the virus; for example, inoculations were made at 11 days, rather than at 9 days, which would permit a longer period of development for normal tissue elements. For this reason in a few preliminary experiments, fragments have been taken from masses recovered at 16 days, after inoculation at day 11, and transferred to new 11-day-old hosts. The recovery of muscle elements was improved in only a few embryos; on the contrary, in most embryos the muscle cells were "swamped out" or overgrown by sarcoma.

A negative finding also has been recorded. In experiments like those described for cardiac muscle attempts to induce kidney structures in the chorioallantoic membrane employing kidney microsome-Rous virus combinations failed. Are these negative findings meaningful? The experiment does not follow one of the tenets established at the outset of the work, namely that the virus and normal tissue have some affinity. It may be necessary to combine kidney microsomes with an appropriate virus from a renal tumor.

Finally, Ebert has cited for comparison two previously existing reports. Oker-Blom and Standström (1956) added to the chorioallantois Rous sarcoma virus mixed with either crude fresh muscle extract derived from the suckling mouse or a mouse muscle extract partially purified with Bentonite. The experiments were performed with another goal in mind (i.e. as controls for mixtures of Rous Coxsackie viruses), and only a passing comment is made about the masses that were recovered, to the effect that they were typical of the tumor. Second, a positive report: Van Haeften (1958) added to the chorioallantois a saline homogenate, said to be free of intact cells, of striated muscle of the adult chicken. It is reported that within 2 days spindle-shaped cells showing the characteristics typical of myoblasts appear, which after another 10 days acquire the features of more mature mononuclear myocytes. They lack cross-striations, yet are believed by Van Haeften to be muscular in nature.

Also of more than passing interest are the findings of Benitez, Murray, and Chargaff (1959) who have demonstrated a heteromorphic change of areolar fibroblasts from the adult rat as a consequence of culturing them in the presence of homologous kidney or liver microsomes. The fibroblasts tended to elaborate a great number of extremely fine processes. The effective agent

is found in the deoxycholate-insoluble fraction of the microsomes, and appears related quantitatively to the amount of RNA added. RNAase destroys much of the effectiveness of the agent. Hence the factor differs sharply from the nerve-growth promoting protein isolated from the mouse salivary gland (Cohen, 1958, 1959; Levi-Montalcini, 1958, 1959).

The latter factor, which can be isolated from mouse sarcoma, snake venom, and mouse submaxillary gland, is believed to be a protein for its activity is destroyed by proteolytic enzymes. It is antigenic, and its specific antiserum inhibits its biological activity. Injection of the growth factor into the chick embryo or into newborn mice results in remarkable increases in the sympathetic ganglia of injected animals, there being net increases in protein, RNA, and DNA. Conversely the injection of the specific antiserum into newborn mice, rabbits, and rats results in near total destruction of the sympathetic ganglia suggesting a role for such a protein growth factor in normal development or maintenance of the ganglia.

Clayton and Okada (1959) have employed the combined action of specific anti-organ sera and RNA in an attempt to reveal specific effects of RNA on embryonic cell populations, it being hoped that the antisera might modify the cell surface as well as inhibit the pathways of normal development, permitting the cells to be channeled into new directions more easily. Treatment of cultures of chick embryo cartilage, heart, and mesonephros with absorbed, specific antisera produced differential effects, depending on the age of the cells, ranging from cell destruction through inhibition of outgrowth to heteromorphic changes comparable to those described by Benitez et al. Addition of RNA prepared by the phenol method from adult chicken brain, heart, or kidney to inhibited cultures produced specific restoration of growth (e.g., addition of heart RNA would restore growth to inhibited heart cultures but not to inhibited kidney cultures) or heteromorphic changes. A few putative specific transformations were recorded; for example, culture of somite cells treated with kidney RNA contained "tubuloid" structures.

One of the principal difficulties in studies of embryonic induction has been that of evaluating a qualitative end point. Recent advances in our grasp of the chemistry of the microsomal particles and their role in protein synthesis suggest more strongly than ever before that recombination experiments involving exchange of microsomes or other subcellular units offer intriguing possibilities for students of development.

MATURATION OF THE IMMUNE RESPONSE

As has become apparent in the course of discussion, we are attempting to raise new questions rather than provide answers to old ones. The cross fertilization that we are encouraging for virology and developmental biology has been paralleled recently by the transfusion of virology and microbial genetics into immunology. In this last section we propose to explore results of this combined microbiological-immunological approach as applied to development of a particular class of proteins, antibody globulins. Although the impact of immunology on developmental biology has been considerable, perhaps the addition of the ideas of viral and bacterial genetics will make the approach more penetrating.

The development of defense mechanisms by the organism involves maturation of several different types of abilities, for not only circulating protein antibodies but also cell mediated reactions, including delayed hypersensitivity, play an important role. The maturation of the immune response has been treated in recent reviews (Ebert and DeLanney, 1960; Lawrence, 1959), and we shall restrict ourselves to recent developments in three areas germane to our inquiry: (1) some developmental aspects of current theories of antibody formation; aspects of graft-host interactions have been treated earlier and except for occasional digression to mechanisms of homograft immunity we shall limit the discussion to development of circulating antibodies; (2) the maturation of the immunological response; (3) the relation of immunological tolerance and antibody formation to current theories on the genetic and epigenetic regulation of protein synthesis in bacteria and viruses.

Theories of Antibody Formation

Theories of antibody formation have been reviewed extensively in the light of newer findings (Burnet, 1959a; Lederberg, 1959; Talmage, 1959). In general, however, a dichotomy exists between two general classes of hypotheses. According to the first, an antigen induces forma-

tion of a complementary reacting protein, the antibody, possibly by a mechanism of complementary folding with the antigen or a template-like derivative; in the second, the antigen selects and stimulates a pre-existing line of cells to produce specific antibody. Burnet (1959a), and Lederberg (1959) have set forth the evidence which stimulated elaboration of the clonal selection hypothesis. Jerne (1955) has also proposed a theory in which antibodies are formed spontaneously under genetic control, the antigen-antibody complex being engulfed and stimulating synthesis of the same antibody rather than selecting clones. It is important to note at the outset that some hypotheses postulate a segregation of antibody forming capacity among competent cells, either by hypermutability of loci determining antibodies or some other undefined process (genetic randomization). As a restatement of the familiar problem of differentiation, the hypothesis must be examined critically.

It has been argued that the clonal selection hypothesis demands that during development the organism must acquire the ability to produce a staggering variety of specific antibodies and that to account for the specificity of antibodies, for example, one must at some stage postulate an influence of the antigen in molding the configuration of the antibody. According to this point of view the selection of pre-existing clones having such an array of possibilities is highly unlikely. Whether one considers an antibody to be a specific and unique stereospecific reactor or a population of combinations of a finite number of configurations (Talmage, 1959), it is becoming increasingly evident that organisms do have the innate capacity to produce molecules capable of reacting with a variety of antigens. We do not understand all of the implications of the existence of these molecules, nor is there evidence from statistical approaches bearing on the possibility that antibody activity results from combinations of a finite number of configurations. The kinds of problems before us are illustrated by the studies of lectins (reviewed by Makëla, 1957), which reveal that many plant seed extracts have highly specific properties as erythrocyte agglutinogens.

One line of evidence bearing on clonal selection theories, while not critical, is the number of antibodies made by one cell. Lederberg has stated that on the basis of the clonal selection hypothesis one would expect at the most two antibodies produced by one cell (in heterozygotes), but this argument assumes that there is one simple locus per cell for globulin synthesis. The basis for this assumption is not made clear. The fluorescent antibody technique for antigen and antibody localization has been employed to examine the number of antibodies made by one cell (Coons, 1958). Although the results are preliminary, multiple immunization of rabbits to egg albumin and diphtheria toxin shows that the number of cells making antibodies against the two antigens equals the sum of fluorescent cells staining for each antibody separately; thus, if any cells make two antibodies, they must be very few in number. White (1958) has examined rabbits immunized with streptococci and ovalbumin by methods utilizing differential fluorescence quenching or two dyes with different fluorescent maxima; he found no cells making antibody against both antigens. Coons and White report that no obvious localized clones of fluorescent cells appear in stimulated animals.

Nossal and Lederberg (1958, see also Nossal, 1959b and c) have developed a technique for testing antibody production by single cells by observing immobilization of *Salmonella* in microdrops by single cells from animals immunized with flagellar antigens of *Salmonella*. Using *S. adelaide* and *S. typhus* antigens for immunizing the rabbits, they found that out of 456 cells tested, 33 were anti-adelaide and 29 were anti-typhus; but no cells immobilized both *Salmonella* species. Nossal (1959b) also has examined the difference between primary and secondary responses; in primary responses only 2.3 percent of the cells yielded antibody, while in secondary response 14 percent of the cells produced antibody. The titer of each cell also increased slightly, from 1.2 to 2.0, but the remarkable increase in the number of cells supports the theory of Lederberg. In contrast to the observations of Nossal, Lennox and Cohn (1959) have demonstrated that a single cell can, and frequently does, make antibody to more than one bacteriophage serotype. Inasmuch as the data of both Nossal and Lennox and Cohn are convincing, why the discrepancy in findings? The evidence does not permit a conclusion; but it should be pointed out that in addition to the obvious difference in antigens employed, the animals used by Lennox and Cohn were hyperimmunized; those of Nossal were not. Moreover

their serial immunization schedule leaves ample time for mutation to occur.

Antibody Formation During Development

It is now generally agreed that with few exceptions circulating antibodies are confined to the globulin serum fraction, especially the gamma globulins. Studies of the synthesis of gamma globulin are hampered by the fact that transmission of maternal serum proteins to the embryo may take place. Nevertheless, it seems that the capacity to synthesize gamma globulins arises late in development, probably near hatching or birth (cf. Ebert and DeLanney, 1960). Studies on man and guinea pigs (Josephson and Gyllensward, 1957; Dancis and Shafran, 1958) support the conclusion that the ability to form gamma globulin appears only after birth and rises gradually to adult levels. Deichmiller and Dixon (1960) have shown the neonatal rabbit gradually acquires the ability to incorporate S^{35} sulfate into gamma globulin. It is a matter of crucial importance to know if animals form any gamma globulin in the absence of antigenic stimulation. Although the matter cannot be decided at present, the recent findings with germ free vertebrates are of interest. Certain natural antibodies, e.g., anti-human erythrocyte B of chicks, arise in germ-free animals only when antigen 0–86 of *E. coli* is present in the autoclaved food. On the other hand, anti-rabbit erythrocyte antibody is present in the absence of any known antigenic stimulation, but the existence of antigens in the diet must be carefully controlled (Wagner, 1959 cf. Springer, Horton and Forbes, 1959). Wostmann (1959) finds greatly reduced gamma globulin levels in germ free chicks, rats, and swine, and none at all in guinea pigs. Whether low gamma globulin levels result from residual antigenic contamination of the food has not yet been ascertained. If no gamma globulin is found in the absence of antigens (and this will be difficult to prove critically because small amounts could easily escape detection), a severe restriction is imposed on theories of antibody formation positing spontaneous development of small numbers of predetermined globulin configurations (cf. Ebert and DeLanney, 1960).

Formation of antibody globulin by isolated cells in vitro is a sensitive process, and transplantation studies also have suffered considerable difficulty from this cause. Indeed, it seems that a rather "favorable" environment is needed for globulin production. Dixon and Weigle (1957) have stimulated debate by reporting that the neonatal rabbit is not a favorable site for antibody production. Is there, then, a maturation of the environment for antibody production in addition to, or instead of, gradual acquisition of cellular capacity for globulin synthesis? Dixon and Weigle (1957, 1959; Dixon, Weigle and Deichmiller, 1959) using lymph node transplantation techniques developed by Harris and Harris (1954; Harris, Harris, and Farber, 1954, 1959) examined the antibody response of stimulated lymph node cells transferred to neonatal hosts. The Harrises had shown previously that if lymph nodes of preimmunized animals were transferred to nonimmune hosts then antibody formation would ensue, the maximum titer being recorded in 3 to 5 days after transplantation and in proportion to the number of living cells transferred. Originally Dixon and Weigle transferred adult node cells to 5-day-old rabbits and x-irradiated adults, noting little or no antibody response in the young rabbits if the cells were transferred within 24 hours after antigenic challenge. But fair titers resulted if one waited 3 days before carrying out the transplantation. X-irradiated adult recipients showed better antibody formation in comparable experiments. Furthermore, injection of labeled antigens demonstrated delayed antigen clearance in neonatal rabbits corresponding to lack of antibody formation. This result would not be expected if the antigen were inducing an enzyme rather than stimulating antibody formation. Further experiments confirmed these results, and Dixon went on to transfer neonatal cells (from 4- to 14-day-old rabbits) challenged in vitro with *Shigella* antigen to neonatal or x-irradiated hosts. No antibody formation was apparent in neonatal hosts, but in half of the adults significant titers (mean 1/457) appeared. These experiments support the hypothesis that there is a maturation of the environment for antibody response in addition to acquisition of globulin synthesis. However, in other systems there is a body of evidence that the embryo is a suitable site for antibody production and for cellular immune responses. In recent reviews (Ebert, 1959a; Ebert and DeLanney, 1960), the evidence has been summarized

more fully than is possible here. It will suffice to point out that adult chicken spleen cells, that have been preimmunized in vivo and inoculated into the chick embryo produce antibody (Sibal and Olson, 1958), and that when adult homologous spleen cells are inoculated into the 18-day-old embryo or newborn chick with antigen, they produce antibody (Papermaster, Bradley, Watson, et al., 1959).

The latter workers argue that the failure of Dixon and Weigle's system stems from variable homograft reactions of the chimera (graft versus host, host versus graft). However, Dixon, Weigle, and Deichmiller (1959) report that this relationship cannot account satisfactorily for their findings because cells transferred to x-irradiated adults lose the ability to respond to antigen injection (presumably because of host against the graft reaction) faster than cells transferred to young rabbits. Considerable recovery of a host against the graft reaction cannot be dismissed in these later experiments of Dixon, and it is best to consider the issue still open, especially in light of the report of positive findings by Harris, Harris and Farber (1959). Perhaps the recent experiments by Nossal (1959a) point the way to resolution of the problem. Using both mice and rats he mixed adult spleen cells with *Salmonella* antigen in vitro, neutralized with immune serum, washed the cells, and then injected them into acceptor animals, bleeding 6 to 16 days after transplantation. Heated cells were used as controls. Host rats less than 2 days old showed no antibody production, but 7 to 11 day old rats produced fair titers. The same situation was present if the recipient was x-irradiated, making a homograft reaction improbable. Hall Institute strain mice behaved like the rats, but in 10 of 12 C_3H strain mice fair antibody titers were observed in very young hosts. If the adult donor rats were stimulated with antigen in vivo, and subsequently rechallenged in four weeks, before transfer in vitro, no difference was observed for this secondary response in hosts of different ages. Neonatal cells transferred to x-irradiated adults or neonatal hosts produced no antibody if the hosts were neonates, but one-half of the adult hosts gave a mean titer of 1/457 after 13 days. On the basis of these results Nossal suggested that the environment supporting antibody synthesis and the ability of plasmacytes or other cells to produce gamma globulin may be two separate, if interconnected, events that mature at different rates; and these two rates may differ in different species and strains. It is known that the effective period for establishing tolerance to homografts differs in various species, so that Nossal's thesis seems reasonable. The conflicting results have been obtained in experiments carried out in different strains and species. One might suggest from Nossal's work that proper attention to details will resolve the difficulties. The type of cell transferred, the type of antigen used, the species used as host and donor, the present and future immunological status of host and donor cells, and suitability of the host for growth and differentiation of donor cells are all factors that have to be considered in interpreting these results. It seems probable that, quantitatively at least, there is a stage in development when conditions for antibody formation are not as good as in adults.

We have treated the development of the immune response largely as if the capacity to receive an antigenic stimulus and the capacity to respond were inseparable in space and time. We must now raise the question whether these two stages are, in fact, separable. Let us consider first separability in space. The argument that the production of antibody requires teamwork of two or more cells of different types has been advanced repeatedly (Ebert and DeLanney, 1960; Wissler, Fitch, La Via, et al., 1957).

Solution of the problem hinges on obtaining a suitable system for study, in vitro. Although many attempts have been made to obtain primary responses in vitro, only recently have Stevens and McKenna (1958) reported success. The experiments depend on previous injection of rabbit donors with endotoxin from *Salmonella typhus*, (a lipopolysaccharide). Twenty-four hours later diced spleen was mixed with antigen (gamma globulin or casein) and cultured by the method of Trowell. In 24 hours measurable antibody (titer 1/82, or 1.4 μg. antibody/ml.) appeared in the culture. If serum from rabbits previously injected with endotoxin was used in the culture medium, the titer could be increased nine times. Endotoxin pretreatment in vitro for 5 hours was also effective, but simultaneous exposure of the cells in vitro to endotoxin and antigen was not successful. Cortisone in vitro inhibited the response, and the response was specific for the antigen used.

Fishman (1959) has demonstrated the pro-

duction of antibodies against T_2 bacteriophage and against hemocyanin in cultured lymph node cells from normal rats. Here we consider the T_2-anti T_2 system as an example. It was necessary that the virus be added first to a suspension of rat cells taken from a peritoneal exudate obtained 48 hours after the intra-peritoneal injection of beef infusion broth. These cells are largely macrophages. After washing and packing the macrophages exposed to the virus are homogenized and the homogenate passed through a Seitz filter. When the resultant cell free filtrate is added to rat lymph node cells in vitro, the latter are stimulated to produce antibodies (as revealed by phage neutralization) within 5 days at 37°C. Neither rat macrophages nor bacteriophage added to the cells singly are effective stimuli. In the bacteriophage-macrophage system, the rat macrophages cannot be replaced by rabbit macrophages or HeLa cells; they can be replaced, however, by a homogenate of rat macrophages.

Finally let us consider whether the ability to recognize an antigenic stimulus is acquired at the same time as the ability to respond.

The spleen of the normal chick embryo, even during the latter quarter of the incubation period, appears to be incapable of a homograft response as judged by its failure as a donor for the graft-versus-host reaction. When fragments of spleen from 17-day-old embryos are grafted to the chorioallantoic membrane of 7- to 9-day-old hosts, the latter develop normally. Ebert (1951) reported a slight, but significant increase in the size of the hosts' spleens which he interprets now as a host response to the graft. Ebert and DeLanney (1960) and independently, Simonsen (1957), on the contrary, in a smaller number of experiments, recorded no effect whatsoever. There are no pathological lesions in the spleens or other organs. Does the inability of the embryonic spleen to effect the reaction result from its inability to respond? Ebert and DeLanney (1960) transplanted fragments of adult chicken heart to the chorioallantoic membrane of 7-, 9-, or 11-day-old hosts. It was known from numerous earlier experiments and amply verified in the current series, that heart grafts are incapable of exerting a graft-versus-host reaction, unless the graft contains a "nest" of immunologically competent cells. Only four such exceptions are recorded in well over 600 heart grafts. Six to eight days after the initial grafts, second-set grafts were established in normal embryonic hosts. Fragments of 17-day spleen taken from embryos having borne heart grafts were transferred. These spleens were normal in appearance and size. Suitable controls were employed, including sham operations, grafts of normal 17-day embryonic spleen, grafts of adult chicken spleen, and for comparison, grafts of embryonic spleen taken from recipients of first-set adult spleen grafts. The results were consistent, many of the second-set grafts exerting an effect on the host spleen. In contrast to a mean host spleen weight of 12.7 mg. following grafts of normal 17-day spleens, the second-set grafts of spleen following a primary heart stimulus produced host spleen weights averaging 16.1, 18.8, and 12.2 mg., respectively. In the last series, the initial stimulus was 6 rather than 8 days. Of these host spleens nine presented the cystic condition characteristic of the graft-versus-host reaction.

Can these findings be explained on the basis of the graft-versus-host reaction? Are they the result of transfer of a small population of immunologically competent cells from the graft? It was mentioned earlier that in only four embryos out of several hundred studied has a recognizable graft-versus-host reaction been observed following a graft of heart (ventricle). Is it possible, however, that in most heart grafts, the incidence of active cells of the immune series is very low, requiring the longer period afforded by transfer to a second embryo to exert their effects? This explanation is made unlikely —but not ruled out—by the fact that the appearance and size of the host spleen following heart grafts is remarkably consistent with the pattern in the normal embryo. There is no suggestion of the proliferation of even a small population of donor cells or of a mild effect on the host liver or spleen.

These considerations lead Ebert and DeLanney to conclude that the findings cannot be explained on the basis of graft-versus-host reaction. Moreover, the results are not those which might have been expected from a consideration of actively acquired tolerance, namely that if the graft influences the embryo's immune mechanisms, that influence should have been in the direction of tolerance. Immunological tolerance is specific with respect to isoantigens, thus tolerance would have been demonstrable only if the second-set (spleen) graft were made to an em-

bryo of the same inbred line. By the same argument, however, since the stimuli for immunity and tolerance are the same, the only difference being the time at which the stimulus is administered, true second-set immunity would not be expected. Is it possible that the findings are due to a stimulus only of the first stage in the immune reaction, namely the stage at which foreign material is engulfed or fixed (it is difficult to employ a term that does not imply a mechanism) before the antigenic message reaches the responding cell? Thus the role of the first-set graft may parallel the role of the beef infusion broth employed by Fishman to evoke the production of macrophages, i.e., it effects a mobilization of the initial receptors.

Immunological Tolerance and Specific Inhibition of Protein Synthesis

Recent advances in biochemical genetics have sharpened the fundamental dichotomy between the classical theories of antibody formation and formation of other proteins. If the clonal selection hypothesis prevails, the apparent operational similarity between antibody formation and the synthesis of other proteins, especially enzyme induction, becomes so striking it is difficult to ignore (cf. Tanenbaum, Mage, and Beiser, 1959). We have already discussed aspects of maturation of immunological capacity. We now intend to briefly review basic aspects of another facet of development of immunological capacity, tolerance, discussing the self-marker concept, tolerance to tumors, a comparison of cell and cell-free induced tolerance, and a consideration of the mechanism of tolerance. Possibly developments in studies on enzyme induction and host cell-virus relations may help to clarify the conceptual and experimental approach to understanding antibody formation.

Any explanation of antibody formation must account for the important phenomenon of immunological tolerance: injection of antigen during a critical period near birth or hatching may suppress specifically the antibody response to subsequent antigenic challenges (Billingham, 1958). The finding that antigenic stimulus at a critical period in development leads to partial or complete breakdown of homotransplant immunity strengthened the self-marker concept; an organism does not begin to form antibodies against its own tissues. More direct support for this thesis has appeared recently. In the first place, Chutna and Haskova (1959) have shown that isoantigens eliciting the homograft reaction are present as early as 8 days in CBA mouse embryos. Terasaki (1959) has shown that in the chicken adult type isoantigens are detectable by the fourth day of embryonic life. Even so, the embryo does not destroy itself. Paterson (1958) and Svet-Moldavsky and Svet-Moldavsky (1959), respectively, have shown that tolerance to isoantigens can be induced in the case of allergic encephalitis. Presumably because of the privileged vascular and immunological site of the central nervous system, the developing immunological system never learns to recognize some antigens of its own central nervous system.

Some workers (Cannon, 1957; Cannon and Longmire, 1952; Cannon, Terasaki, and Longmire, 1957) have maintained, however, that tolerance is an adaptation of the graft to the host rather than the development of host mechanisms. This finding, based primarily on the difference in success of homotransplants from newborn or embryonic donors and adult donors, possibly may be explained by the recent finding of Billingham and Silvers (1959) that adult chicken skin is immunologically competent in causing a graft-against-the-host reaction when grafted to the chick chorioallantoic membrane; but newborn skin elicits no such reaction, presumably because the immune elements become tolerant to the host. Agammaglobulinemics retain at a reduced level the cellular immune reaction, delayed hypersensitivity, but are not capable of producing circulating antibody nor of giving an antibody dependent immediate hypersensitivity reaction (Porter, 1956). Good (1956) has demonstrated that homotransplants to agammaglobulinemic patients will persist for long periods, but the transplantation of the agammaglobulinemic skin to normal hosts results in prompt graft rejection. It is puzzling that agammaglobulinemia leads to homograft establishment, since presumably only production of circulating antibodies is inhibited; perhaps the lesion is more pervasive than supposed. However, the available evidence indicates only that cells are a necessary participant in graft rejection; their participation may not be sufficient, however, and soluble factors may be a necessary adjunct in the reaction. The precise relation of transplantation immunity to delayed hypersensitivity has only begun to be investigated, but the results of Brent, Brown, and

Medawar (1959) augur well for the future. They found, utilizing a guinea pig homograft system, that a delayed type inflammatory response accompanied secondary intradermal injection of lymph node cells from donor to host, or vice versa, and this effect was not transferable by serum.

We have considered the question of heterotransplantation of tumors in immunologically immature animals. Once established in the immature animal, tumors commonly persist beyond the time at which resistance normally would be manifested. In other words, the tumor has induced a state of tolerance. For example, Puza (1959) transferred Crocker's mouse sarcoma to newborn rats, and found that it persisted. In extending the earlier experiments of Duran-Reynals and others, Svoboda and Grozdanovic (1959) have analyzed the heterotransplantation of the Rous sarcoma in young rats. Svet-Moldasvky (1957, 1958) described adaptive changes in the virus associated with the formation of hemorrhagic cysts following the inoculation of rat embryos and newborn rats with sarcoma homogenate, and Kryukova (1959a) injected newborn rabbits with a suspension of frozen sarcoma and observed fibromatous nodes. Svoboda and Grozdanovic (1959) found that all young rats inoculated from birth to 4 days after birth with a single intraperitoneal injection of sarcoma tissue died from circulatory lesions accompanied by characteristic cysts. Neither virus extracts nor normal chicken tissue were effective. Rous sarcoma virus was found only rarely.

More puzzling are the reports (e.g., Harris, 1956) that the injection of normal tissue into embryos or newborn animals produces a state of tolerance which later permits the growth of tumors of the donor "strain." For example it is reported that the injections of chicken blood into turkey embryos, resulting in a state of tolerance, later permits the growth of the Rous sarcoma virus, leading to tumors with characteristic metastases. These findings have been confirmed by Svoboda (1958). Tolerance to heterologous Crocker's mouse tumor was induced successfully in rats by an analogous method (Grozdanovic, 1959).

One of the more difficult problems in this field is to determine whether tolerance to homografts and unresponsiveness to heterografts and noncellular antigens represent the same or similar phenomenon (recently considered in extenso by Ebert, 1959a). It seems clear now that long term unresponsiveness to soluble antigens and heterologous erythrocytes can be established, and the specificity and length of the unresponsiveness suggest that possibly the basis for the phenomenon is the same as homograft tolerance. Recent reports of unresponsiveness to defined antigens (Curtain, 1959; Smith and Bridges, 1958; Tempelis, Wolfe, and Mueller, 1958a and b; Terres and Hughes, 1958) add to the weight of the earlier reports by Dixon and Maurer (1955), Cinader and Dubert (1956), and Hanan and Oyama (1954). In addition, induction of unresponsiveness to heterologous erythrocytes in rats (Nossal, 1957), and persistent turkey-chicken chimeras (Hasek, Hraba, and Hort, 1959) have been reported. Haskova and Majer (1959), however, have shown that an aqueous extract of chick spleen will confer transplantation immunity, but fails to induce tolerance; and Hort and Hraba (1957) showed that administration of very large doses of plasma was necessary to produce tolerance in newborn chicks. Although Kerr and Robertson (1954) reported tolerance to *Trichomonas foetus* in seven calves and Buxton (1954) reported a reduced response at 118 days to *Salmonella pullorum* antigen in chicks injected in ovo at 15 days, Sterzl and Trnka (1957) found no tolerance in 5-day-old rabbits injected with *Salmonella paratyphus*.

Although the status of bacterial antigens is still far from clear, the number of reports stating that reduction or abolition of response to an antigen ensues if a first injection is made near birth leaves no doubt as to the reality of the phenomenon; and in some cases (Cinader and Dubert, 1956; Curtain, 1959; Dixon and Maurer, 1955; Smith and Bridges, 1958), the reduction has been shown to be specific for the particular antigen in question. However, as has been pointed out elsewhere, the abolition is rarely complete, usually disappears in time, and requires large antigen doses. We must remember, though, that the dose used with living cells also is quite large and that some of the population of foreign cells take up sites in the host and remain there. It is doubtful, in fact, that all the cells disappear, so that the host is constantly exposed to antigen.

When comparing unresponsiveness to defined antigens and tolerance to homografts, it is important to determine if continued presence of antigen is necessary for maintaining both of

these types of unresponsiveness. Injection of an antigen at very early stages may not result in tolerance (Buxton, 1954; Cohn, 1956b). Could the antigen have disappeared before a critical period? Tolerance to homotransplants is reduced or abolished if the original transplant is removed (Medawar and Woodruff, 1958), and Billingham (1958) has concluded that when tolerance is present a cell chimera also is present. Billingham and Brent (1957) found this state held invariably in experiments using isogenic mouse strains. Recently Mitchison (1959) induced unresponsiveness to radioactive chromium-labelled erythrocytes in chicks and found that unresponsiveness disappeared completely when all the cells disappeared from the host. The evidence for soluble antigens points in the same direction. The very thorough study of Smith and Bridges (1958) showed that unresponsiveness to bovine serum albumin in rabbits is proportional to the amount of antigen injected and the number of times injected; when all the antigen is cleared, unresponsiveness disappears. Yet, homologous lymph nodes transferred to unresponsive animals respond quite well to the antigen, ruling out the possibility of antigen excess neutralizing the antibody. Tempelis et al. (1958a and b) obtained similar results with dose-response studies on bovine serum albumin in chickens. It seems, then, that chimeras are a sufficient condition for stable tolerance (however, homotransplantation tolerance is not an all or none reaction), and that large repeated doses of soluble antigens are needed to produce unresponsiveness; both findings suggest that the presence of the antigen is needed for tolerance. Homograft tolerance may not be absolutely individual specific (Kulangara, Cannon, and Longmire, 1959), nor is heterotransplantation (Hasek et al., 1959). The specificity of responsiveness to non-cellular antigens can be quite good (Cinader and Dubert, 1956; Smith and Bridges, 1958) and also may extend to cross-reacting serum proteins (Curtain, 1959). It seems to be a fair working hypothesis that specific unresponsiveness induced near birth or hatching, regardless of the type of antigen, takes place by similar mechanisms.

Of unusual interest in considering the suppression of antibody formation are the experiments of Wyttenbach (1960). Wyttenbach injected newborn rabbits with saline homogenates of chicken liver or spleen. At 11 weeks, the animals were challenged with the homologous homogenate. By precipitin tests, positive control animals (previously uninjected) gave titers of 2000 and 6400 respectively; the corresponding experimental groups gave average titers of about 200. In a different group of rabbits not challenged until later (20 weeks), response was suppressed but not as greatly. When both the spleen-antispleen (control and experimental) and liver-antiliver systems were studied by the Ouchterlony technique, sera of all experimental ("tolerant") rabbits gave several *more* bands than the positive controls.

Wyttenbach suggests that both spleen and liver contain a small number of antigens which are present in higher concentration, or are more strongly antigenic, so that upon primary exposure to the whole homogenate, the control rabbits produce antibodies against only these molecules. Adler (1957) and Oudin (1958) among others have reported cases of such competition among antigens. It is further suggested that for the very reason that these evoke the greatest primary response, they are also the most apt to effect tolerance when the homogenate is injected into the newborn. Consequently, rabbits tolerant or even partially tolerant to these major components will, upon challenge, respond to a variety of lesser components. This argument is supported by the observation that very few of the antisera from the experimental animals produced precipitate bands corresponding in appearance and position to the bands from the antisera of control rabbits. Wyttenbach argues that his findings point to a suppression of antibody formation. The doses of antigen employed have been too small to account for the duration and the degree of tolerance by neutralization of antibody. All sera collected immediately prior to challenge showed no antibody. At the age of 11 weeks, all rabbits were challenged with 75 mg per kilogram body weight of homologous antigen, amounting to approximately 125 mg per rabbit. Thus, up to the time of collection of antisera, the average rabbit had received 150 mg of antigen and the controls 125 mg, a difference of just 20 percent. Wyttenbach believes it unlikely that this small a percentage difference in the total antigen received between the control and experimental rabbits could account for the difference in titers of circulating antibody by a means other than the suppression of antibody formation.

Wyttenbach refutes the argument that a small amount of tissue-fixed antigen could effect such a result if one visualized a single molecule of antigen as capable of neutralizing many antibody molecules without itself being altered. As he says, if this were true, then the plot of serum titer against time following the last injection should show a greater rate of decay for the experimental rabbits than for the controls. Yet no such difference was observed. Finally, he emphasizes that interpretation of his findings in terms of the neutralization of antibody by tissue-fixed antigen does not satisfactorily account for the more diverse response on the part of the experimental rabbits.

The mechanism of the establishment of tolerance is itself a subject of paramount importance, for here the developmental biologist has a tool for specific inhibition of protein synthesis, an invaluable adjunct to studies on differentiation of protein components of cells. Furthermore, an understanding of the mechanism of tolerance may well give us clues about the development of proteins other than antibody. In this last section we intend to discuss various possibilities for explaining tolerance and to consider some evidence from microbiology, which when combined with our previous considerations of tolerance, suggests an explanation of tolerance.

Of the several types of explanations for tolerance, one may list: (1) all the developing antibody-forming cells are sensitive to antigen and die when exposed to this antigen; (2) there are several clones of antibody-forming cells, each making a particular globulin stereo-configuration; each clone is hypersensitive, during its development, to its complementary configuration and dies when exposed to it (Lederberg, 1959); (3) antigen inhibits intracellular globulin-synthesizing machinery so synthesis of some specific globulins are inhibited; (4) an antigen destroys all gamma globulin synthesis of a clone by a mechanism similar to 3; (5) antigen continuously reacts with newly formed antibody and inactivates it; or (6) antigen stimulates an inhibitor of antibody production (cf. Ebert and DeLanney, 1960). In addition these hypotheses may be combined and modified in many ways. Crampton, Frankel, and Rodehaver (1959) have proposed that the antigen-antibody complex stimulates intracellular proteases which diminish or eliminate antibody formation. This interesting hypothesis still awaits a critical test. Denhardt (1960) has suggested that antigens may induce "secretases" during neonatal life, and these secrete the antigen out of the cell preventing antibody formation. Recent evidence (Crampton, et al., 1959; Garvey, Eitzman, and Smith, 1960) on the distribution of antigen in tolerant and non-immunized animals does not conform with the predictions of this hypothesis.

Hypotheses five and six seem unlikely in the face of the transfer experiments of Smith and Bridges (1958) and adoptive transfer (transplantation of immunologically competent but unimmunized cells to a tolerant animal) experiments of Billingham (1958). And the first possibility seems unlikely because of the specificity of tolerance. Thus, we are left with distinguishing between cell death or specific inhibition of protein synthesis without cell death. Even though there is strong evidence that cells participate in homograft rejection, it does not bear critically on the question of cell death versus inhibition of protein synthesis. And, as stated before, it has not been shown that only cells are involved in homograft rejection; both hypotheses have their merits. It is difficult to explain the need for continuous presence of antigen on the clonal-cell death hypothesis unless new stem cells are constantly developing and passing through this sensitive phase. Specific inhibition of protein synthesis without cell death links antibody formation, be it in clones or not, closely with other well observed cases of induced protein synthesis, e.g., inductive and repressed enzymes.

Let us examine next the phenomenon of immunological tolerance in the light of recent studies on enzyme induction and repression.

Although the evidence for the phenomenon of enzyme repression has been at hand for many years, only recently has the detailed experimentation by several groups of investigators made the extreme importance of the phenomenon apparent (cf. review by Pardee, 1959). In an operational sense enzyme repression is the opposite of enzyme induction; administration of a compound, usually related sterically to the substrate or product (however, glucose inhibits induction of a host of enzymes; cf. review by Magasanik, 1957) leads to a reduction in the rate of net synthesis of an enzyme. Apparent enzyme repression may result from a "feed-back" type mechanism; the product of a biosynthetic

pathway inhibits the *activity* of a previous enzyme in the pathway, [cf. Gots (1957) on purine metabolism; other cases reviewed by Pardee (1959)]. But cases of true repression of net synthesis are more important for our present purposes. Yates and Pardee (1957) have demonstrated that synthesis of three enzymes concerned with pyrimidine synthesis in *E. coli* are repressed by uracil. Gorini and Maas (1957) report arginine inhibits the synthesis of ornithine transcarbamylase, and Vogel (1957a) has shown arginine inhibits synthesis of acetyl ornithinase. More recently Gorini (1960) has shown ornithine competitively counteracts the repressive action of arginine on ornithine transcarbamylase, i.e., ornithine is an inducer under certain conditions. Magasanik (1957) has obtained results showing repression in purine synthesis, and Adelberg and Umbarger (1953) have proposed a similar mechanism for accumulation of alpha-oxoisovalerate in some mutants of *E. coli*. Vogel (1957b) has presented a unitary mechanism for explanation of induction and repression of enzyme formation. He proposes that the crucial step in enzyme synthesis is the dissociation of nascent enzyme from the enzyme-forming template, and that inducers and repressors act at this step, either increasing or decreasing the rate of dissociation.

A series of experiments of considerable importance bearing on this problem have recently issued from the Pasteur Institute. Previously Monod and his co-workers (Monod and Cohen-Bazire, 1953a and b; Cohn, Cohen and Monod, 1953) had demonstrated that tryptophane (and indole) inhibits formation of tryptophane desmase in *Aerobacter aerogenes*; β-galactosides repress formation of β-galactosidase in constitutive mutants of *E. coli*, and methionine exerts a similar action on formation of methionine synthetase of *E. coli*. Moreover, Jacob and Campbell (1959) have offered evidence that lysogenic immunity in *E. coli* is a repressor type phenomenon exerted by a cytoplasmic inhibitor.

The recent brilliant experiments by Pardee, Jacob and Monod (1959) on the genetics of inducibility of β-galactosidase in *E. coli* have extended these findings. The conversion from inducible to constitutive for both β-galactosidase and permease, a specific transport system, is a single event at the "i" locus, i^+ being inducible and i^- constitutive. The "i" gene regulates the activity, or expression of the y^+ and z^+ (ability to make permease and enzyme, respectively) loci, and has been called a regulator gene. This conclusion was reached by examining enzyme formation in merozygotes of reciprocal crosses of z^+i^+ and z^-i^- genotypes in the absence of inducer. By utilizing auxotrophs as receptor cells, occurrence of cytoplasmic mixing was ruled out; the zygotes, which do not segregate for several hours, contain only the cytoplasm of the receptor cell, but chromosomes of both parents. Streptomycin sensitivity and susceptibility to T-6 bacteriophage infection were used to follow recombination and kill donor cells to prevent remating. When z^+i^+ is the donor, enzyme formation in the absence of inducer begins a few minutes after the entry of the z^+ gene and continues for about 90 minutes, but then ceases. However, addition of inducer at this time will allow enzyme formation to continue at the same rate. If z^-i^- is the donor and z^+i^+ is the receptor, there is no enzyme formation whatsoever in the absence of inducer. Pardee, Jacob, and Monod feel that this finding probably signifies that the i^+ gene elaborates and releases into the cytoplasm an inhibitor of the manufacture of β-galactosidase (or, may stimulate a catabolic system destroying β-galactosidase; cf. Dubnoff, 1955). The inducer must somehow inactivate this inhibitor. These remarkable experiments strengthen the idea that repression and induction may be due to one basic mechanism, and that regulator genes may play a vital role in regulation of protein synthesis during epigenesis. (See Pardee and Prestidge, 1959 for a discussion of the nature of the repressor of β-galactosidase synthesis.) More recent work by Jacob, Perrin, Sanchez and Monod (1960) has added another complex and sophisticated chapter to this story. During the synthesis of β-galactosidase by *E. coli* the regulator exerts its apparent pleiotropic action at the genetic level by repressing another closely linked gene, "O". "O" is called the operator and controls the expression of other nearby loci belonging to the same biochemical sequence ("y" and "z" in this case). The entire unit of the operator and the genes whose expression it controls is called the operon. Although the repressor apparently acts directly at the genetic level in this instance, as the authors point out, it may, a priori, also exert its repression at the level of cytoplasmic replication of the operon.

These considerations suggest immediately a

striking parallel between enzyme repression and immunological tolerance. The change from a repressed, inducible enzyme to a constitutive one is a single gene change, at least for β-galactosidase. The change from tolerant to responsive is a matter of a few days Billingham (1958). Both changes are a shift from a specific repressed state to a state where specific protein synthesis is stimulated. The following set of postulates is intended to propose a mechanism for tolerance, but they may also apply to origin of proteins other than gamma globulin during development.

1. Each cell potentially capable of making antibody spontaneously produces a specific globulin type (or types), the time and type of molecule produced being genetically determined. Homograft rejection also depends on the elaboration of a specific protein, which may not, however, be a soluble globulin. This postulate demands a segregation of antibody-forming capacity during development, either by mutation (Lederberg, 1959) "randomization" (Burnet, 1959a) or most simply, by unequal distribution of cytoplasmic genetic elements.

2. In the case of antibody formation, some induced enzymes, and possibly other proteins, the control of synthesis is vested in two genes. One locus contains all the information needed for the synthesis of the protein. The second, a regulator locus, controls elaboration of a specific regulator substance which either (a) inhibits the formation of the protein-forming machine, (b) more probably inhibits the activity of the protein-forming machine (Magasanik, Magasanik, and Neidhardt, 1959), or (c) as in the case of β-galactosidase acts directly on an operator gene controlling the expression of the gene for synthesis of the protein.

3. The action of inducer or antigen (or its metabolic derivative) is to combine with and/or inactivate the regulator, thereby releasing the protein-forming machine to maximal activity. In addition, there may be a stimulation of cell division, as suggested by Lederberg (1959) to explain the larger response to a secondary antigenic challenge.

4. In the absence or diminution of the regulator, the inducer or antigen (or a metabolic derivative thereof) may interfere with the synthesis or activity of the protein-forming machine, thus producing a state of tolerance. The absence or diminution of regulator may come about because the rate of production of regulator may be quite low during the time of first expression of the regulator gene.

It should be pointed out that none of these postulates have any claim to originality. Although they assume a great deal, even if they are far from correct, perhaps they will stimulate an examination of the phenomenon on the genetic level. The central theme of postulate one has already been clearly presented by Lederberg (1959), although the present authors must take responsibility for the thesis that homograft rejection involves formation of specific protein by the host. Postulate two is derived from the ideas and conclusions of Pardee, Jacob and Monod (1959) on β-galactosidase of *E. coli* merely applied to antibody formation; and postulate four is an interpretation reached by consideration of some studies on repressible constitutive enzymes. Although it is usually the product of a constitutive enzyme which represses enzyme synthesis (and this makes for an effective metabolic control mechanism), the available evidence suggests that in certain cases the sterically related substrate may also exert repressive effects, just as we are suggesting here. Conversely, there is no a priori reason why the product of an enzymatic reaction might not be an inducer.

Although this particular theory demands rigid stereospecific conditions, so do most chemical events of biological importance. The postulates impose certain restrictions on the stereospecific relations of the three components, antigen, regulator, and enzyme-forming machine, but these relations cannot be clearly stated without a more detailed knowledge of the mechanism of protein synthesis. Recent work by Cohen and Jacob (1959) on enzyme repression suggests, however, that the regulator has a substrate-like molecule as part of its structure.

On the basis of these postulates, tolerance would follow if antigen were administered early in the development of antibody response mechanisms. For each antibody-forming gene there is a regulator gene, which comes into play later or more slowly than the antibody locus. Administration of antigen produces specific inhibition of antibody formation in the absence of sufficient regulator (however, not all protein-forming machines may show substrate inhibition; again, it depends on delicate stereospecific requirements and the exact mechanism of pro-

tein formation). Continuing inhibition of antibody formation requires continued presence of antigen.

This mechanism poses two questions which must be answered. First, why doesn't enzyme repression or tolerance follow administration of very large quantities of antigen or inducer even in the presence of regulator? It appears, in fact, that this effect is found in some cases (Dixon and Maurer, 1955; Felton, Kauffmann, Prescott, et al., 1955). Three factors tend to reduce the probability of this occurrence: (a) the rate and specificity of possible transport systems will regulate the internal concentration of inducer or antigen so that large external concentrations fail to produce large internal concentrations; (b) action of preformed enzyme or antibody will neutralize excess antigen or inducer as soon as it gains access to the cell; (c) the concentration of regulator substance may be so high it will be difficult to overload.

Second, after regulator begins to appear in large quantities during development of antibody forming cells, one might expect repression or tolerance to diminish unless extremely high concentrations of antigen are present. Perhaps, however, the protein-forming machine has a greater affinity for the antigen than does the regulator, or is irreversibly damaged by it. It would be interesting to determine the history of enzyme formation in crosses of $z^+i^+ \rightarrow z^-i^-$ in the presence of high concentrations of inducer from the beginning of the entry of z^+ into the receptor cell, a situation formally comparable to the explanation proposed here for tolerance. One would expect a long lasting diminished rate of enzyme formation.

After this article had been written, two articles by Szilard (1960a, b) appeared in which the phenomenon of enzyme repression is discussed in relation to cell differentiation and antibody formation. Although his postulates are too detailed to examine fully here, it is important to state that he utilizes similar formal elements in his theory, enzyme-forming machines, antigens, and repressors. His introduction of other elements, such as coupling enzymes which synthesize repressors, results in certain differences in the exact mechanisms of tolerance and antibody formation, but the emphasis on repressors and repressor genes is similar to that presented here.

Since the foundation of this scheme of tolerance is genetic, critical proof must come from experiments bearing directly on the genetics of somatic cells, and antibody-forming cells in particular. Perhaps the recent advances in animal virology and mammalian cell cultures will enable genetic operations to be carried out. But until this becomes possible, certain types of experiments can at least provide evidence either detrimental or favorable to the point of view presented here. First, specific inhibition of antibody protein synthesis would not necessarily lead to cell death, as posited by the hypersensitivity hypothesis of Lederberg. Fluorescent antibody could be used to observe directly antigen localization during tolerance induction (cf. Secary and Coons, 1959) and comparison made with occurrence of cell death. Second, injection of extremely high concentrations of hapten or antigen could lead to specific unresponsiveness in adults in some cases, especially in tissue culture systems. Third, a biochemical search for a regulator substance might be made, being assayed by its ability to inactivate or modify the antigenicity of the antigen in question in vitro. More critical experiments can be devised when transfer of genetic information from cell to cell, especially in tissue culture systems, becomes possible.

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A GENE CONCEPT BASED ON GENETIC AND CHEMICAL STUDIES IN NEUROSPORA

By DOW O. WOODWARD

Microbiology-Cellular Biology Branch, School of Aviation Medicine, Brooks Air Force Base, Texas

ABSTRACT

Two methods of analysis of the fine structure of genes are discussed. These methods yield data that support the concept of linear organization within a gene. This organization is apparent in both genetic and complementation maps. Experiments designed to give information concerning the mechanism of complementation are described. These data indicate that it is possible to simulate complementation in vivo. In this case complementation in vivo in Neurospora crassa is characterized by the ability of two ad-4 mutants growing together as a heterocaryon to produce functional adenylosuccinase, which neither mutant can make when grown alone. The simulated complementation occurs in vitro by mixing partially purified and presumably differentially defective forms of mutant adenylosuccinase. Maximum efficiency of complementation in vitro is obtained when attempting to modify or interchange —SH and —S—S— bonds of the protein. Theoretically, such a treatment could result in the formation of aggregates, hybrid molecules, or complexes of various forms. It is postulated that if this means of restoring enzyme activity is the mechanism of complementation in vivo, then the complementation map is a reflection of the structure and properties of the enzyme rather than the gene. The similarities between genetic and complementation maps can be accounted for by a template model for the gene-protein relationship. This theory also explains occasional discrepancies between genetic and complementation maps, since such maps presumably correspond respectively to the structure of different macromolecules, DNA in the former case, protein in the latter.

INTRODUCTION

EARLY work of Beadle and Tatum (1941) laid the foundation for a more precise formulation of the concept of a gene-protein relationship. Currently, the concept in broad terms appears to be widespread in application. A number of advances during the past two decades have supported the idea that a definite correlation exists between a gene (DNA) and the enzyme protein under its control. The exact nature of this correlation is not known, but a number of models have been suggested (see Yanofsky and St. Lawrence, 1960). Further attempts to investigate the gene-protein relationships include studies of structure and function of genetic material. A number of recent reviews (Pontecorvo, 1958; Wheeler, 1958; Demerec and Hartman, 1959; Fincham, 1959a; Beadle, 1960; Yanofsky and St. Lawrence, 1960) adequately discuss various aspects of gene structure and function. Only a very limited area of the overall gene concept will be treated here. The primary topics to be emphasized in this paper include studies dealing with gene structure based on two independent methods of analysis, and studies of gene function based on the behavior and characteristics of their protein products. The only specific implication intended in the title of this paper is that the following discussion will be restricted primarily to investigations with *Neurospora crassa*. Whether there are basic differences in gene structure or function among different organisms is beyond the scope of the present review.

TERMINOLOGY

Out of necessity, it has become almost standard procedure in publications on genetic fine structure to define the terms used in describing the substructure of a gene. This paper is no different in that respect, since the number of terms in existence is continually increasing, and provides a wide selection from which to choose a system of nomenclature. The advisability of using Benzer's (1957) basic terminology in this paper will be apparent. The following diagram indicates how this terminology applies in a hypothetical situation (see Fig. 1). The cis-trans test in *Neurospora* interallelic heterocaryons reveals units distinguishable from the "Benzer cistrons." Functional units can be resolved by the cis-trans test in *Neurospora* that are continuous in the sense that some mutants are non-functional in more than one unit; i.e., many mutants appear to have overlapping defects. These units, then, will simply be called complementation units.

A gene must be redefined from the classical "unit of crossing over" when applied as in Fig. 1, but regardless of how a gene is defined, the fact remains that a region of the genetic material controlling the formation of a single protein is subdivisible by various analyses. Gene loci that have been subdivided by such analyses are sometimes referred to as "complex loci" (see Carlson, 1959; Demerec and Hartman, 1959 for recent reviews) although all loci may, in this sense, be "complex" as more detailed studies of their fine structure are made.

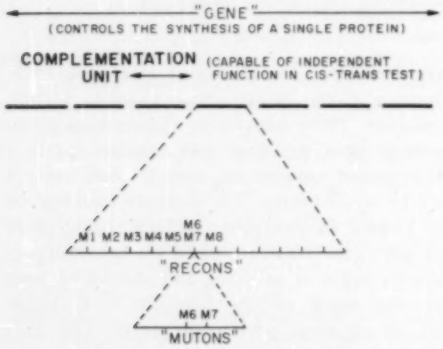

FIG. 1. HYPOTHETICAL GENE SUBSTRUCTURE

A gene can be subdivided into complementation units capable of independent function and these in turn into smaller units between which genetic recombination occurs. Mutants that do not yield recombinants show still other differences, e.g., different reverse mutation rates, ability to complement other alleles, etc.

GENETIC FINE STRUCTURE

The first successful attempts to study locus structure in *Neurospora* were made by genetic analyses in which large populations and selective screening methods were used to detect rare recombinants between allelic mutants (Bonner, 1951; Giles, 1951). During the past decade, similar studies have been made at a number of loci (see Pontecorvo, 1958; Demerec and Hartman, 1959).

It has been possible, in detailed genetic analyses of this type to map recons (units of recombination) within a gene in linear order (Benzer, 1957). Case and Giles (1960) have mapped a minimum of 27 different recons within the *pan-2* locus in crosses involving 34 mutants. A minimum of 13 recons were found at the *pyr-3* locus in a study involving 34 mutants (Suyama, Munkres, and Woodward, 1959). Similar maps have been obtained from genetic analyses at various other loci in *Neurospora* (Bonner, 1960; Webber, 1959; see Demerec and Hartman, 1959). There are exceptions to linearity, and the additivity is not completely consistent; nevertheless, such analyses are suggestive of linear arrays of recons within these loci.

It must be remembered that there are several possible sources of error in making analyses of genetic fine structure. The major difficulties involve reversion, gene conversion, and the formation of pseudowild-type colonies. If the reverse mutation rate of either of two mutants is comparable to the frequency of prototrophs arising by recombination, large errors result unless it is possible to distinguish the revertants from the recombinants. This is very difficult to do in *Neurospora*. Pseudowild formation (presumably disomics) is a problem, almost unique to *Neurospora*, when crosses between complementing mutants are analyzed for recombinants. The pseudowild colonies can usually be detected, but when they outnumber the true wild-type colonies by 100 or 1000 to one, it is difficult to analyze the cross. Gene conversion can be detected by tetrad analyses, but if tetrads are used there is still a problem of selection for

or against certain types of tetrads unless there is complete maturation and fertility of ascospores. The most formidable barrier, however, is the work involved in tetrad isolation techniques. It is difficult to isolate a sufficient number of tetrads to obtain a population large enough to make accurate measurements of recombination frequencies in the 0.001 per cent range or beyond. In the case of gene conversion, there is evidence of a relationship between recombination frequency and gene conversion, such that a linear order is established by pooling prototrophs derived by both mechanisms (Case and Giles, 1960; Suyama, Munkres, and Woodward, 1959). It is still possible that only one mechanism is responsible for all prototrophs that have been placed into categories labeled "gene conversion" ("non-reciprocal recombination") and "reciprocal recombination."

COMPLEMENTATION

A second method of studying gene substructure, independent of genetic analyses, involves an examination of *Neurospora* functional units. This was made possible by the discovery of interallelic complementation (Giles, Partridge, and Nelson, 1957; Fincham and Pateman, 1957). The test for complementation in a heterocaryon between two mutants is based on the cis-trans comparison that was first used by Lewis (1951) to study position effects in *Drosophila* heterozygotes. The trans relationship is ordinarily the only part of the test used in *Neurospora* complementation studies.

Basically, the test is made by putting two types of mutant nuclei of independent origin in a common cytoplasm. The resulting heterocaryon is then observed in order to determine the extent of restoration of the functional defect which the mutants exhibit when grown separately. Benzer (1957), in referring to the cis-trans test as a means of detecting functional independence in bacteriophage, stated: "A functional unit can be defined genetically, independent of biochemical information, by means of the elegant cis-trans comparison. . . . Such a map segment corresponding to a function which is unitary as defined by the cis-trans test applied to the heterocaryon will be referred to as a cistron." By comparison with the complementation units of *Neurospora*, it appears likely that the "Benzer cistrons" are separate but closely linked genes having perhaps biochemically related, yet biochemically independent functions. If this is indeed true, there appears no compelling reason to retain the term cistron at all as it applies in this situation. It is true that difficulties have arisen in attempting to modify the definition of a gene as more detailed information is obtained, but this problem is not solved by replacing the term "gene." In much the same way as a taxonomist finds difficulty in defining a species, yet recognizes what the term specifies, geneticists by analogy have done likewise with the gene.

If the term cistron is retained to apply only to complementation units, a modification of the specified application would be required. The alternative would be to coin a new term for the complementation units. The extent of the differences between "Benzer cistrons" and *Neurospora* complementation units cannot be completely resolved until the phage *rII* gene product or products are characterized.

Based on complementation maps representing various loci in *Neurospora*, a number of observations have been made. The patterns of complementation which have been described in terms of complementation maps order the mutants of a locus in a one-dimensional linear sequence (Woodward, Partridge, and Giles, 1958; Lacy and Bonner, 1958; Catcheside and Overton, 1958). The linear arrangement is possible because of the existence of mutants with overlapping defective regions. The *ad-4* complementation map is composed of 10 such linearly arranged complementation units (see Fig. 2). This complementation map includes mutants having from one to nine defective or non-functional complementation units. In addition to the complementing mutants, more than half of the available *ad-4* mutants are completely non-functional in the trans configuration, and fail to complement any other *ad-4* mutant.

There is, in general, agreement between genetic and complementation maps in the ordering of mutants (Case and Giles, 1960; Rachmeler, Ph.D. thesis, Stanford University, 1960; Yanofsky, 1960; Webber, 1959). Exceptions to co-linearity between the two kinds of maps do appear, however. De Serres (unpub.) now has evidence for rather extensive non-linearity in the complementation pattern at the *ad-3* locus in *Neurospora*.

Another general observation is that non-complementing mutants are distributed across the

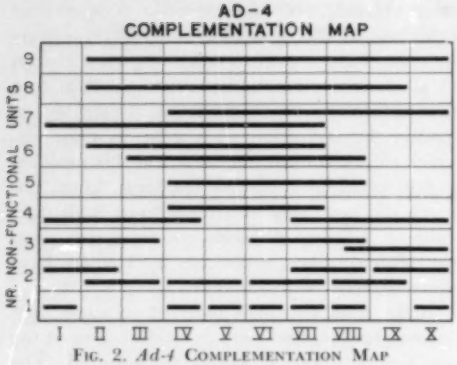

FIG. 2. *Ad-4* COMPLEMENTATION MAP

Each solid line in this diagram represents one or more mutants. It also represents a defective or non-functional region of that mutant or mutants based on the ability or inability to complement other *ad-4* mutants. Thus, overlapping lines represent non-complementing combinations that do not produce detectable adenylosuccinase activity when grown as heterocaryons.

entire genetic map, a fact indicating that they do not result from damage at only one specific region within the locus (Case and Giles, 1960; Suyama, Munkres, and Woodward, 1959). There are also non-complementing mutants that are genetically indistinguishable from complementing mutants. Based on an analysis of a minimum of 10^5 ascospores, two *pyr-3* mutants (one complementing, the other non-complementing) have defects within a single recon (Suyama, Munkres, and Woodward, 1959). In addition, mutants occupying a short genetic segment may overlap several complementation units (Woodward, Partridge, and Giles, 1958; Case and Giles, 1960; Suyama, Munkres, and Woodward, 1959).

A correlation has been shown between the biochemical properties of mutants and their indicated positions on the complementation map (Wagner, Somers, and Bergquist, 1960; Webber, 1959). The two examples indicating this type of correlation appear to be somewhat unique in a functional sense in that two enzymes are specified, and the complementation map that corresponds is continuous between the two regions. Wagner and coworkers have demonstrated that the transformation of the beta-keto acid precursors of isoleucine and valine to the alpha-keto acid precursors involves three chemical steps which are carried out by two enzymes. Furthermore, there appears to be genetic overlap in the region controlling the formation of these two enzymes such that a mutation which corresponds to the center of the overall region affects both enzymes. Webber's (1959) data indicate a similar type of overlap, in that a mutation in the center of the complementation map results in the loss of two enzyme activities in the histidine pathway. The latter example differs from the former in that the two reactions are not sequential.

There are indications of a correlation between distance on the complementation map and the efficiency of complementation as measured by growth rates, enzyme activity, or both, restored in the heterocaryons (Woodward, 1959; Case and Giles, 1960; Wagner, Somers, and Bergquist, 1960). Certain heterocaryons appear to be exceptions to the general pattern (see Fig. 3), but in general, heterocaryons formed between mutants at the two extremes of the complementation map yield higher enzyme activities than those adjacent to each other. The data from *ad-4* mutants shown in Fig. 3 combine comparable distances (based on the number of complementation units) over the entire complementation map and represent 36 different heterocaryon combinations. An additional source of variation is that the enzyme activity is influenced by the mutant used. Some mutants give characteristically low activities in all combinations, while others are comparatively high.

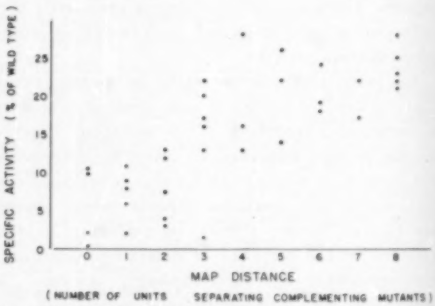

FIG. 3. RELATIONSHIP BETWEEN COMPLEMENTATION MAP DISTANCE AND ADENYLOSUCCINASE ACTIVITY in *ad-4* INTERALLELIC HETEROCARYONS

Each point represents a different heterocaryon between various pairwise combinations of *ad-4* mutants. The only heterocaryons that are not included with these data are five heterocaryons involving adjacent complementation units. Growth of these heterocaryons was not sufficient to make an assay for adenylosuccinase activity; therefore, it is assumed that the level of enzyme activity was less than one percent of wild type.

All of these data have been pooled. It should also be noted that the maximum level of enzyme activity restored in these heterocaryons is approximately 25 per cent of wild type. This maximum level of restoration of activity is not exceeded by interallelic heterocaryons at other loci (Pateman and Fincham, 1958; Megnet, 1959; Lacy, 1959). It has also been shown that enzymes produced as a result of complementation differ from the wild-type enzyme in some cases (Fincham, 1959b; Partridge, unpub.). These differences have been detected primarily as differences in thermostability and metal ion sensitivities.

A final point of importance is that among mutants lacking activity for the enzyme tryptophan synthetase, all of the complementing mutants are capable of forming a cross-reacting protein related to the normal enzyme (Bonner, 1960; Yanofsky, 1960).

THE MECHANISM OF COMPLEMENTATION

These separate observations, although seemingly unrelated in some instances, are helpful in intrepreting the complementation map and possibly in relating the structure of DNA and protein to their respective functions. Based on some of these observations, hypotheses were proposed to explain the mechanism of complementation in terms of gene product interactions, since nuclear change during the asexual cycle of *Neurospora* has never been detected (Woodward, Partridge, and Giles, 1958; Catcheside and Overton, 1958; Pateman and Fincham, 1958). The types of interactions proposed to account for interallelic complementation included RNA-RNA, RNA-protein, protein-protein, and protein-activator or protein-inhibitor systems.

A recent study (Wainwright, 1960) of protein synthesis in cell-free extracts from *Neurospora crassa* conidia suggests the cytoplasm as the site of the defective component of a *td* mutant. The defective component was localized in the soluble fraction not sedimented by centrifugation at $105{,}000 \times g$ for one hour.

An interaction at the RNA level would lead to a requirement for protein synthesis in order to produce active enzyme. Recent studies of complementation in vitro between adenylosuccinaseless mutants revealed no detectable net protein synthesis under the conditions used to recover enzyme activity when homogenates from two complementing mutants were mixed. Furthermore, there were no significant differences in the amount of enzyme activity recovered when either chloramphenicol (500 μg/ml) or crystalline ribonuclease (64 μg/ml) was added to the mixture (Woodward, unpub.).

The demonstration of complementation in vitro (Woodward, 1959) makes an interaction at the protein level seem reasonable if complemen- exchange during the asexual cycle of *Neurospora* tation in vitro is indicative of the mechanism of complementation in vivo. Several types of protein-protein interactions were alluded to earlier (Woodward, Partridge, and Giles, 1958; Woodward, 1959). These included the following basic types: (1) dissociation and reassociation of a mixture of polypeptides giving, in effect, recombination to yield hybrid protein (Singer and Itano, 1959; Crawford and Yanofsky, 1958); (2) formation of hybrid protein by interchanges involving peptide linkages as in the case of subtilisin-treated ribonuclease (Richards, 1958); (3) formation of an aggregate or complex as suggested by the work on hemoglobin-haptoglobin complexes (Harris, Robson, and Siniscalco, 1958; Bearn and Franklin, 1958). Models based on some of these examples predicted a maximum restoration of 25 per cent of wild-type enzyme activity. This would also include aggregation or dimerization, assuming it to be an obligatory and random dimerization with a one-way correction between the two defective proteins. A one-way correction in this case is the correction of only one of the active sites in a dimer composed of two differentially defective proteins, each with an active site. This prediction is also based on the assumption that the ratio of nuclei contributed by the two complementing mutants is approximately 1:1 and that the total amount of defective protein produced is quantitatively equivalent to the enzyme protein of the wild-type strain.

The work of Pittenger and Atwood (1956) suggested the possibility of accomplishing a study of the quantitative effect on enzyme activity by varying the nuclear ratios in heterocaryons. They demonstrated that in heterocaryons between non-allelic mutants a nuclear ratio, once established, will remain constant even when a change in nuclear proportions would be advantageous. Interallelic heterocaryons between *ad-4* mutants were established by the same method (Pittenger and Atwood,

TABLE 1.

NUCLEAR RATIOS IN AD-4 INTERALLELIC HETEROCARYONS

	CONIDIAL INPUT RATIOS	NUCLEAR RATIOS AT END OF 12" GROWTH TUBE	GROWTH RATE MM / HR
AD-4 F54/M8PAN	.0004	9	3.8
	.004	3	3.9
	.04	7.3	3.9
	.4	6.5	3.8
	3.8	7.5	3.9
	38	5.6	3.3
	380	1.5	3.4
	.0006	1.2	3.4
	.006	2.1	3.4
	.06	1.3	3.0
	.6	1.9	3.8
	5.9	7	3.9
	59	5	3.0
	590	25	4.0
AD-4 F4/M8PAN	.0001	1	3.0
	.001	3	3.2
	1	1	3.6
	100	6	3.5
	1000	45	3.4

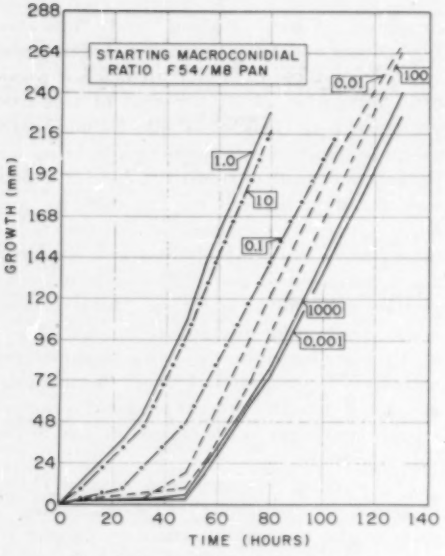

FIG. 4. GROWTH RATES OF AN *ad-4* INTERALLELIC HETEROCARYON

Growth rates are plotted for heterocaryons between mutants F54 and M8 *pan-2* (double mutant) with conidial starting ratios ranging from 0.001 to 1000 (F54/M8 *pan-2*). Note the relationship between starting ratio and growth lag. Final growth rates are approximately the same regardless of the starting ratio.

TABLE 2.

NUCLEAR RATIOS IN AD-4 INTERALLELIC HETEROCARYONS

AD-4 HETEROCARYONS	CONIDIAL INPUT RATIOS	NUCLEAR RATIOS AT END OF 12" GROWTH TUBE
F31/F5PAN	6	3
	0.0006	2
F1/F4PAN	180	0.49
	0.018	0.30
F5/F4PAN	130	0.66
	0.013	0.07

1956) at ratios ranging from 0.001 to more than 1000. The skewed ratios were not maintained (see Table 1). Measurable growth ceased for as long as 50 hours after heterocaryosis became obligatory (Fig. 4). The lag time was proportional to the ratio of the two nuclear types, i.e., the lag time increased as the ratio deviated farther from 1:1. When growth finally commenced, the rates were the same regardless of the starting ratio. Heterocaryons with low yields of adenylosuccinase activity were also studied (Table 2). The data suggest that altered ratios are not responsible for the low activity in such heterocaryons.

Additional studies were initiated with com-

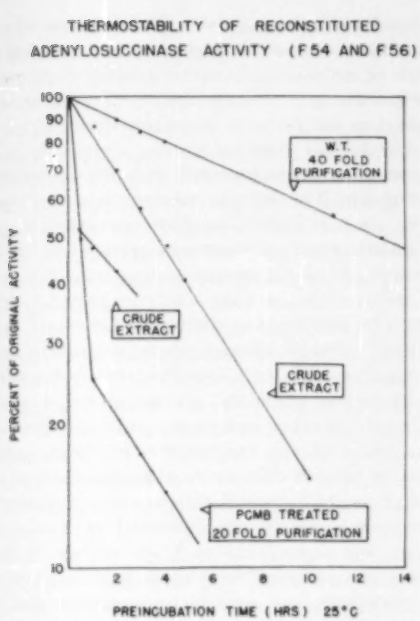

FIG. 5. INACTIVATION OF ADENYLOSUCCINASE AT 25°C

These inactivation plots of reconstituted adenylosuccinase are representative of various experiments. The slopes varied considerably and in some cases showed a definite change in the rate of inactivation after an hour or less at 25°C. Only three inactivation plots are shown for reconstituted adenylosuccinase. These are compared to the inactivation of wild-type (W.T.) enzyme. These three plots illustrate the basic types of decay curves observed; however, there was more variation in inactivation rates than is indicated here.

plementation in vitro in attempting to determine the type of protein-protein interaction which could account for the formation of a functional enzyme from two differentially defective enzymes. A number of theories have recently been advanced (Fincham, 1959b; Yanofsky, 1960; Case and Giles, 1960; Beadle, 1960; Yanofsky and St. Lawrence, in press; Suskind and Yanofsky, in press) as possible explanations.

Adenylosuccinase, reconstituted in vitro by utilizing extracts from complementing *ad-4* mutants, resulted in the recovery of enzymes quite heterogeneous with respect to thermostability (Fig. 5). In some cases, what may be two forms of adenylosuccinase, based on differences in thermostability, were recovered. Variations in the proportions of two forms of adenylosuccinase could account for the apparent differences in the rates of inactivation.

Assays for adenylosuccinase activity were routinely made by observing the change in absorption at 280 millimicrons as the reaction proceeds from adenylosuccinate (AMP-S) to adenylic acid (AMP). However, several checks were made during various experiments by scanning the ultraviolet range. The absorption peak in all cases shifted from 267 $m\mu$ toward 260 $m\mu$ which is characteristic of the adenylosuccinate to adenylic acid reaction. In certain cases, the reaction was not carried to completion by the reconstituted enzyme. This was particularly true if the reaction rate was slow. An incomplete reaction was detected by measuring the change in absorption at 280 $m\mu$ (Fig. 6) or by scanning the UV range (Fig. 7).

There is little or no detectable adenylosuccinase activity in the crude extract when complementing mutant homogenates are mixed after separate extraction. Activity can be recovered, however, by fractionating the mixture on a diethyl-aminoethyl (DEAE) cellulose ion exchange column. The fact that several of the mutant enzymes alone can be partially activated by purification is significant; however, this does not account for all of the activity obtained in the mixture.

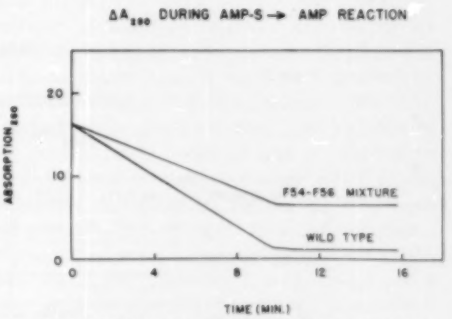

FIG. 6. MEASUREMENTS OF ADENYLOSUCCINASE ACTIVITY

These slopes are reproduced from a time drive measurement of change in absorbance at 280 $m\mu$ on a DK-2 recording spectrophotometer. The amount of substrate (AMP-S) used was the same for both reactions. In some cases the reconstituted enzyme does carry the reaction as near to completion as wild-type enzyme.

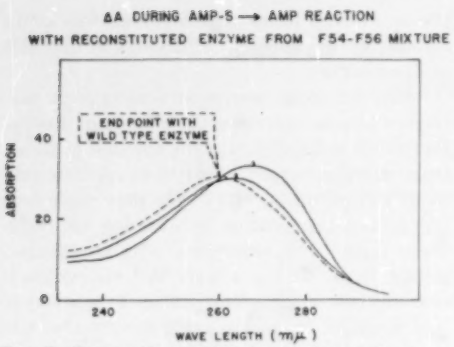

FIG. 7. RECONSTITUTED ADENYLOSUCCINASE ACTIVITY DETERMINED BY REPETITIVE SCAN

A repetitive scan with one sample of reconstituted enzyme from a mixture of mutants F54 and F56 being reacted with AMP-S. The final scan (peak nearest 260 $m\mu$) was as far as the peak shifted in this case. In other cases, using reconstituted enzyme from complementation *in vitro*, the peak shifts to 260 $m\mu$, which is characteristic of the end-point when wild-type enzyme is reacted with AMP-S (dotted line).

POSSIBLE INVOLVEMENT OF DISULFIDE INTERCHANGE REACTIONS

Complementation in vitro has also been accomplished when utilizing mutant enzyme that has been purified approximately 20-fold. This was done under the assumption that the mutant form of the enzyme could be recovered in approximately the same fraction as the wild-type enzyme. Fractions believed to contain mutant adenylosuccinase from the two complementing mutants were mixed. Such mixtures contained little or no detectable adenylosuccinase activity. Fractionating the mixture on DEAE cellulose resulted in the recovery of increased adenylosuccinase activity. Another striking increase in enzyme activity was observed with the following treatment. The enzyme mixture at this point was treated with para-chloromercuribenzoate (PCMB), which is known to react with —SH groups. The concentration used was that required to inactivate the wild-type enzyme (10^{-4} M). The mixture was then passed through the DEAE cellulose column, and the protein recovered was inactive. To the inactive protein fraction was added the amount of 2-mercaptoethanol (or other reducing agent) required to activate wild-type enzyme that has been inactivated by para-chloromercuribenzoate. This resulted in the increased activity. Some representative experiments are illustrated in Table 3. Note that in Experiment 3, an increase in activity was observed even when para-chloromercuribenzoate, and then mercaptoethanol (ME), were added while the reaction was in progress.

Madsen and coworkers (Madsen, 1956; Madsen and Cori, 1956; Madsen and Gurd, 1956) have made a study of structural change accompanying reaction of enzyme sulfhydryl groups. Their results suggested the approach to the study of complementation just described. They have demonstrated that muscle phosphorylase

TABLE 3.

ADENYLOSUCCINASE ACTIVITY

$(\Delta A_{280} / \text{MG. PROTEIN} / \text{MIN.} / \text{ML.})$

TREATMENT	MUTANT	EXPT. 1	EXPT. 2	EXPT. 3*	EXPT. 4	EXPT. 5
CRUDE EXTRACT	F54	.000				000
	F56	.000				000
↓	F54 – F56			20 MIN. LAG .005	.000*	
0.1M-0.3M KCL FRACTION	F54	25 MIN. LAG .025	25 MIN. LAG .025		8 MIN. LAG .095	25 MIN. LAG .080
	F56	.040	.000		.060	.000
(DEAE CELLULOSE)	F54 – F56			8 MIN. LAG .330	8 MIN. LAG .160*	
↓	F54				.105	
PCMB → DEAE → ME	F56				.050	
	F54 – F56			DURING REACTION .525	.270*	.420

* EXTRACTED TOGETHER

in the presence of para-chloromercuribenzoate is cleaved into four equal parts which are inactive. When there is 50 per cent inhibition of enzyme activity, it also causes 50 per cent dissociation to the monomer. The loss of enzyme activity proceeded more slowly than the reaction with para-chloromercuribenzoate; i.e., the enzyme retained activity after all 18 sulfhydryl groups had reacted. This is probably due to continued structural change following reaction with para-chloromercuribenzoate leading to inactivation, dissociation, and finally denaturation, in that order. The loss of enzyme activity and the dissociation to four monomers are both reversed by cysteine. These investigators suggest that other groups besides the sulfhydryl group keep the four parts of phosphorylase associated and that removal of the sulfhydryl groups produces an unstable molecule.

It should also be pointed out, as Lumry and Eyring (1954) have mentioned, that proteins should not be considered as existing in only one definitive configurational state, but various parts of the molecules may be expected to undergo more or less randomly small conformation changes. With such conformation changes, sulfhydryl groups may be temporarily exposed for reaction, the result being that the more stable conformation cannot again be assumed. Repetition of such an event can lead to gross structural change.

The results of complementation in vitro are compatible with the idea that differentially defective enzymes could associate to form an active or partially active aggregate. Perhaps the monomers actually combine to form the active site of the enzyme. If the adenylosuccinase system is similar to muscle phosphorylase, the association of defective proteins may involve disulfide interchange reactions. The reasons for not achieving still higher recoveries of enzyme activity after manipulating disulfide and sulfhydryl groups of adenylosuccinase is probably due to insufficient purification of the enzyme, since in crude extract the treatment is completely ineffective. Another possible difficulty in getting optimal activity in vitro may be that a slow process of rearranging ordinarily takes place in vivo, and experiments in vitro are too short to get maximal recovery of enzyme activity. The loss of ability to get reconstituted enzyme activity is rapid; consequently, it is a race to purify the mutant enzyme protein before complete inactivation or denaturation occurs. At any rate, there are numerous examples in the literature that suggest a process by which existing disulfide bonds in proteins are disrupted and new disulfide bonds are formed. Mazia (1958) has even proposed that the structure of the mitotic apparatus may involve the polymerization of protein molecules through a glutathione-initiated disulfide interchange reaction (Jensen, 1959).

CONCLUSIONS

The combined results of various workers on complementation in vivo and in vitro suggest that a complementation map is a functional map—of the enzyme protein directly—and of the gene controlling that enzyme indirectly. Complementation units, even though they reflect the linear organization of the gene, appear to be determined by the structure and characteristics of the enzyme. If this is indeed the case, it should not be surprising to find loci at which none of the mutants exhibit interallelic complementation, simply because of the physical properties of the enzymes controlled by these loci. For example, enzymes that form aggregates may complement each other while those that do not have this property may represent groups of mutants that do not complement each other. Assuming this relationship to be valid, what then is the explanation for the widespread occurrence of non-complementing mutants at loci in which complementation occurs? Based on the views presented here, it could be explained by the location of the genetic defect rather than by the type of genetic defect. The location of the genetic defect would in turn correspond to an amino acid residue or residues which would ultimately determine its ability or inability to complement. For example, let us assume that a defect in the genetic material of a non-complementing mutant specifies a substitution for a cysteine residue or for any amino acid critical to the proper folding configuration of the protein. Such a change could exert a drastic effect on protein structure by rendering it incapable of interacting (complementing) in the cytoplasm. The change could thus affect a large portion of a protein which phenotypically would be interpreted as damage to more than one complementation unit based on the complementation map.

This may explain how a presumed "point mutation" localized in a small genetic segment can be defective or non-functional in more than one complementation unit. In other words, the mutation affects a small genetic region which may specify a critical amino acid and thereby result in a large defect in the protein.

The concept of a gene and of the relationships between structure and function that have been presented in this paper support a template model of gene action. It is felt that further progress in this area of genetics will depend to a large extent on detailed studies of purified enzymes.

ACKNOWLEDGMENTS

The views expressed in this paper are those of the author and are not to be construed as official Air Force statements of policy.

The author wishes to acknowledge the able technical assistance of Miss Carol Volkmann in certain aspects of these investigations.

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NEW BIOLOGICAL BOOKS

The aim of this department is to give the reader brief indications of the character, the content, and the value of new books in the various fields of Biology. In addition there will occasionally appear one longer critical review of a book of special significance. Authors and publishers of biological books should bear in mind that THE QUARTERLY REVIEW OF BIOLOGY *can notice in this department only such books as come to the office of the editor. The absence of a book, therefore, from the following and subsequent lists only means that we have not received it. All material for notice in this department should be addressed to H. B. Glass, Editor of* THE QUARTERLY REVIEW OF BIOLOGY, *Department of Biology, The Johns Hopkins University, Baltimore 18, Maryland, U. S. A.*

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GENERAL BIOLOGY: PHILOSOPHY AND EDUCATION

NEW BIOLOGY, *No. 31.*
Edited by M. L. Johnson, Michael Abercrombie, and G. E. Fogg. Penguin Books, Harmondsworth (Middlesex), and Baltimore. 65 cents (paper). 156 pp.; ill. 1960.

The biologists of the world have lost a British friend. Number 31 of the Penguin Books' *New Biology* is the latest, and last, issue of this paperback series. The reason given by the editors for discontinuing the series is that the sales of the volumes no longer justify their continuation. I cannot begin to read the implications of this action when science in general, and biology in particular, is burgeoning on all sides, and just when it is widely predicted that the significant scientific achievements of the future will more likely come from the biological sciences than from the physical sciences, which have enjoyed so singular and dramatic a success over the last half century.

The *New Biology* series was initiated in 1945. Its editors since the beginning have been M. L. Johnson and Michael Abercrombie, joined later by G. E. Fogg. In a brief, and wistful, editorial in the last issue, they review their expectations for the series, and regret that their assumption of having a sufficient number of readers turned out to be wrong. Thus dies a remarkable series of little books, for which at present there is no replacement. Biology has had some attention in the Penguin series, *Science News*, which survived 54 issues, but this series too has been discontinued.

Where will we now find in the popular press such intriguing articles as the series on famous animals and famous plants? Where will we read recollections like Haldane's of Karl Pearson? In what pages will we find readable, brief, stimulating articles on Edible Birds' Nests, The Structure of Darwinism, Biting Midges, and The Present Research in Beer?

Throughout these fifteen years the quality of these books has been exceptionally high. Fascinating aspects of modern biology have been presented to the lay and professional audiences with thoroughness, simplicity, and imagination. The reader of these books, with no other sources of biological knowledge, would have a remarkably adequate acquaintance with most of what is significant in biology, both old and new.

This last book of the series, Number 31, is devoted to the central and distinctive problem of biology: replication. All of the articles deal with aspects of biological reproduction, and together they present the forefront of knowledge in this area. J. Brachet has written on the control of protein synthesis, N. D.

Symonds on DNA structure and replication, K. Burton on replication in bacteria and viruses, D. R. Newth on replication during embryogenesis, J. H. Humphrey on antibody formation, G. H. Beale on the problem of differentiation, and finally, N. W. Pirie has considered in a penetrating way some of the epistomological problems raised by a general consideration of biological replication.

All in all, this is a remarkable issue to end a remarkable experiment in science publishing. Just like the editors, we can only hope that the theme of replication will somehow lead to the revival of some filial descendent of this series, at least in spirit, and that it will receive the support it deserves from the biologists, teachers, students, and laymen of tomorrow. Meanwhile, you had better hurry to your bookseller to complete your files with those issues of *New Biology* that you have somehow overlooked. This may be your last chance.

FRANK C. ERK

BIOLOGY: HISTORY AND BIOGRAPHY

MEDIEVAL AND RENAISSANCE MEDICINE.

By Benjamin Lee Gordon. Philosophical Library, New York. $10.00. xiv + 843 pp. + 60 pl. 1959.

It is difficult to review this book adequately in a limited space. Suffice it to say that had it been reviewed in manuscript by experts in the history of medieval and renaissance medicine, it would have either been completely rewritten to reflect the findings of modern scholarship in this field, or better yet, it might never have been published. Since the book, unhappily, is now in print, it is the duty of this reviewer to warn prospective readers to use it with critical caution. It is poorly organized, the transliteration of Arabic names does not appear to follow any recognized scheme such as that of Sarton or of the Royal Asiatic Society, and the text abounds in examples of either sloppy proofreading or downright erroneous spelling, e.g., Loeuwenhoek for Leeuwenhoek, Santrio Santro for Santorius Santorius . . ., ad nauseam. Many footnotes are misquotations or are erroneous in their references to pages and dates. On p. 788, the author quotes Sarton as saying in his *Introduction to the History of Science*, Vol. I, p. 274, 1927, that "Ptolemy's Optics is the most remarkable experimental research in history." What Sarton actually wrote was: "the most remarkable experimental research *of antiquity*" [italics added].

MORRIS C. LEIKIND

CENTAUR. *Essays on the History of Medical Ideas. By Félix Martí-Ibáñez. MD Publications, New York.* $6.00. xx + 714 pp. 1959.

The author of this collection of essays is a most prolific writer whose flamboyant style reflects his Spanish origin. Professor of the History of Medicine at the New York Medical College, Félix Martí-Ibáñez is also an astute and energetic man of business, as indicated by his publishing enterprises, notably the medical news magazine *MD* of which he is the editor. Most of the essays in this book, which may be characterized as a medico-literary smörgasbord, appeared initially in *MD*. They cover a wide range of topics, such as Books in the Physicians Life; Padua and London: a Harveian Tale of Two Cities; Medicine in the World of Don Quixote; The Spirit of American Medicine; Philosophic Perspectives of Motion Sickness; The Challenge of Bio- and Chemotherapy in Psychiatry; On the Psychology of Symbolism in Oriental Rugs; and The Brush and the Bottle: Maurice Utrillo." This sampling should whet the reader's appetite, and the book is recommended for the bedside table.

MORRIS C. LEIKIND

A HISTORY OF SCIENCE, TECHNOLOGY AND PHILOSOPHY *in the 16th & 17th Centuries. Second Edition. Volumes I and 2.*

By A. Wolf with the cooperation of F. Dannemann and A. Armitage; second edition prepared by Douglas McKie. Harper Torchbooks, Harper & Brothers, New York. $1.95 each (paper). [Vol. 1] xvi + 349 pp.; ill.; [Vol. 2.] xv + pp. 350–686; ill. 1959.

These two volumes comprise a paperback reprint of the second edition of Wolf's unique and monumental study. To the encomiums which this studious, lucid, and well-organized compendium received when first published, little need be added at this late date. The work, especially in virtue of its comprehensiveness, and the sheer mass of facts presented, remains an indispensible tool for any student of the 16th and 17th centuries, no matter what his field. Its publication in a relatively inexpensive paperback edition, with the numerous original illustrations included, is commendable.

Nevertheless, in the perspective of over a quarter century (Wolf's original preface was dated 1934), it is possible to enter certain caveats, which, although they are essentially irrelevant to the enduring values of the work, may point to some of the pitfalls into which the time-bound historian is likely to fall.

The philosophical outlook of Wolf's study, for example, perhaps reflecting the intellectual temper of the 1930's, often approaches a polemical positivism. The imposition of this late 19th and early 20th century focus of philosophy on the earlier period works against any successful projection by the modern reader into the intellectual climate of the 16th and 17th century thought. Often, too, Wolf's char-

acterizations of 16th century thought, and of early Renaissance and late Medieval thought are based on the presuppositions of the 19th century historicisms rather than strict historicity. In short, Wolf sees those parts of history which coincide with his scientism as good, and those parts which do not, as bad.

This naive "hero-villain" dichotomy, which specialized historians in any field are peculiarly susceptible to make, not only tends to distort the picture of the historical period they treat but also betrays an incapacity to embrace sympathetically the divergent elements in the complex of any culture.

JAMES J. HILL

A HISTORY OF TECHNOLOGY. *The Industrial Revolution 1750 to 1850. Volume IV.*

Edited by Charles Singer, E. J. Holmyard, A. R. Hall, and Trevor I. Williams; assisted by Y. Peel, J. R. Pretty, and M. Reeve. Oxford, at the Clarendon Press, London. £8 8s. xxxiv + 728 pp. + 48 pl.; text ill. 1958.

Volume IV, of what is indubitably the most stupendous work yet undertaken in the history of science and technology, deals with the period of the Industrial Revolution, designated as c. 1750–c. 1850 although it is still obviously continuing in many parts of the world. As in the other volumes, relatively little emphasis has been given in this one to biological developments in technology. That is not surprising, in view of the overwhelming abundance of advances in other fields demanding consideration; but the fact does afford grounds for a hope that some day we may have a similar comprehensive treatment of the biological technological developments that have marked man's progress from paleolithic times to the present.

This great volume is divided into parts dealing with Primary Production, Forms of Energy, Manufacture, Static Engineering, Communications, and the Scientific Basis of Technology. Of its 23 chapters, written almost exclusively by British authorities, those that come closest to biology are chapters 1 and 2, on Agriculture: Farm Implements and Techniques of Farming, and on Fish Preservation, and chapter 16, on Sanitary Engineering: Water Supply and Sanitation. The all too brief chapter comprising the entirety of Part VI, and dealing with The Beginning of the Change from Craft Mystery to Science as a Basis for Technology (A. R. J. P. Ubbelohde), will interest historians of science in general.

Like other volumes of the *History of Technology*, this one is excellently printed and illustrated. It is supplied with an extensive Index of Personal Names (giving dates and professions) and an Index of Place-Names, as well as the more usual index of subjects, which is uncommonly full and abundantly cross-indexed.

BENTLEY GLASS

MELCHIOR TREUB. *Pioneer of a New Era in the History of the Malay Archipelago. 26th December 1851–3rd October 1910.*

By H. H. Zeijlstra. Koninklijk Instituut voor de Tropen, Amsterdam. Dutch guilders 9.–. 128 pp.; ill. 1959.

In 1951 the Netherlands Royal Topical Institute organized a celebration of the centenary of Melchior Treub's birth; on that occasion H. H. Zeijlstra delievered an address that has been expanded into the present biography. Treub, who was trained in botany at Leiden, became Director of 's Lands Plantentuin (the Government Botanical Gardens) at Buitenzorg in the Netherlands Indies in 1880. He resided in Buitenzorg until 1909, the year before his death. In the absence of universities in the Netherlands Indies, 's Lands Plantentuin was the only botanical research center. Zeijlstra describes Treub's own researches in plant embryology, physiology, and ecology, his development of the laboratory as a research center, and his activities that eventuated in the transformation of the Botanical Gardens into the Department of Agriculture, of which he became the first head in 1905. The biography contains a pedigree of the Treub family, a list of the visiting scientists who worked at the 's Lands Plantentuin during Treub's directorate, and a brief list of sources. The book will be principally of interest to those concerned with the history of administration of botanical and agricultural institutions, but it may also be of more general interest as a footnote on the history of the techniques of colonization.

JANE OPPENHEIMER

ERINNERUNGEN EINES BIOLOGEN.

By Karl von Frisch. Springer-Verlag, Berlin. DM 26. 172 pp. + 1 folded chart; ill. 1957.

Told with simple frankness and charm, these recollections of a great biologist's childhood, his years of study, his family life, and his professional associations create vividly the atmosphere of German scientific scholarship in its golden age. More than any other book, it reminds me of Richard Goldschmidt's *Portraits from Memory*—a matter not surprising, since many of the same places and same people figure in both books. Goldschmidt was in fact a young "Assistent" under Richard Hertwig in Munich at the time when von Frisch began his graduate studies there. The Adriatic and the Zoological Station at Naples also filled a significant place in the training

and development of professional enthusiasm in the lives of both young zoologists.

Through the years of his first professorial appointments, in Rostock, in Breslau, and then in 1924 back in Munich; a first visit to America in 1930; and later through the bitter years of World War II and the quiet, famous work on the bees in Brunnwinkel, the reader moves on to the post-war period in Graz, a second trip to the United States in 1949, and finally the transfer for the fifth time to Munich, where Karl von Frisch has carried on the great tradition of his master teacher, Richard Hertwig.

Unlike many such volumes of scientists' reminescences, this one contains interleavings of the author's researches. Not only the studies of the "language" of the bees, so well-known to English-speaking audiences in translation and popular essay, but other, equally interesting but less familiar researches are given space. I found very intriguing the account of Karl von Frisch's studies for his doctoral thesis, on the capacity of color change in the minnow and its light-sensitive pineal body, and the later work on the ear and eye of the fish. A bibliography, to 1957, is included in the volume.

This is a work that, like an increasing list of others written by Karl von Frisch, well deserves the wider circulation it would receive through translation into English. Meanwhile, let all biologists who are interested not only in technical scientific achievements but also in the making of biologists polish their command of German by some quiet hours with this book. It will reveal not only a fine scientist but human nature at its best. The modest and unassuming guise of the author cannot obscure the glowing spirit of one we are glad to have met.

BENTLY GLASS

VIRUS HUNTERS.

By Greer Williams. Alfred A. Knopf, New York. $5.95. x + 522 pp. + 16 pl. 1959.

This is the story of virology for laymen, built mainly around virologists rather than viruses. The emphasis is upon applied virology, the discovery of viral agents in disease, and the development of vaccines. Retold, of course, are the stories of Jenner and the smallpox vaccine, of Pasteur and the rabies vaccine. This aspect of virology is brought up to date with the story of the polio vaccines and research on "cold" viruses. The debate about a viral cause for cancer is not neglected. The more basic problems of virus structure and mode of multiplication are also described, but not as extensively.

The author attempts to humanize his story by trying to present the virologists he discusses as persons and to describe the "real" roads they followed to discovery. Particularly fascinating are his accounts of how Robley Williams was led to develop the shadow-casting technique for electron microscopy, and of the politics surrounding the use of the Salk polio vaccine. However, in some places in the book, one has the feeling of reading the script of a grade B movie. Also uneven are the accounts of theories and ideas, probably owing to the author's lack of grasp rather than his presentation of the material. These faults are annoying rather than fundamental —on the whole, this is a good book. The author delves into his material to some depth, a fact surprising in a popular book, and the presentation is such that the layman will surely follow the story with fascination and profit.

R. S. EDGAR

THE YOUNG NATURALIST

THE LITTLE NATURALIST.

By Frances Frost; illustrated by Kurt Werth. Whittlesey House, McGraw-Hill Book Company, New York, Toronto, and London. $2.50. 47 pp.; ill. 1959.

A collection of children's verse, mostly about animals. Typically the effect of each poem is to evoke an image, usually sentimental, sometimes "precious," but seldom strikingly original. The level of vocabulary shifts, so that while some of the poems might be suitable for six- or seven-year-olds, other poems will present words difficult for many ten-year-olds. The illustrations are pleasant, but not striking.

JAMES J. HILL

THE WONDERFUL WORLD OF LIFE. *The Story of Evolution.*

By Julian Huxley. Doubleday & Company, Garden City. $2.95. 69 pp.; ill. 1958.

It would be difficult to decide for what sort of reader (or looker?) this book was intended. The book is profusely and magnificently illustrated in color and the illustrations, design, and title of the book all suggest that it was intended for children through the early teens. One feels, however, that Sir Julian Huxley's text, though very sound biology, is paradoxically neither fish nor fowl: neither suitable nor likely to be fully understood by the juvenile audience to which the pictures and format are likely to appeal, nor, in the nature of the case, a full-fledged monograph on evolution, were such conceivable here.

This is a pretty book, but the profusion of beautiful illustrations has no systematic arrangement such as would be likely to convey any coherent ideas about evolution to the young reader, and Sir Julian's

text, the vocabulary of which alternates between the elementary and the sophisticated, is equally unlikely to be intelligible to the average young reader.

JAMES J. HILL

ALL ABOUT THE JUNGLE.

By Armstrong Sperry; illustrated by the author. Random House, New York. $1.95. viii + 141 pp.; ill. 1959.

ALL ABOUT ARCHAEOLOGY.

By Anne Terry White; illustrated by Tom O'Sullivan. Random House, New York. $1.95. vi + 148 pp.; ill. 1959.

ALL ABOUT PREHISTORIC CAVE MEN.

By Sam and Beryl Epstein; foreword by Carleton S. Coon; illustrated by Will Huntington. Random House, New York. $1.95. viii + 137 pp.; ill 1959.

In these three books, Random House continues to maintain the general quality of the "*All About*" series as among the very best science books for children being published in this country. The uniform plaudits which the books have received from responsible journals and organizations seem fully justified. Nor are these recommendations limited to adult critics with formulated opinions as to what is good for children. The books have also received the Junior Book Award Certificate of the Boys' Clubs of America. Judging from the response the books received from several pre-teen-age and early teen-age children to whom the reviewer lent his copies, the award was more than justified.

Each of the three books reviewed here is clearly and interestingly written by a competent writer in the field, and is tastefully and attractively illustrated. Although *All About Archaeology* contains a representative and excellently chosen 12 pages of photographs, the other illustrations in this book, as in the other two books, are very effective, often capturing important details of scenes and artifacts better than could be achieved by photographs. The index in each book further enhances the likelihood that these books may go far toward promoting a serious interest in their subjects among many young people. The scientist who considers writing a book about his specialty for children would do well to peruse a few "*All About*" books as models.

JAMES J. HILL

BEFORE AND AFTER DINOSAURS.

By Lois and Louis Darling; illustrated by the authors. William Morrow & Company, New York. $2.95. 95 pp.; ill. 1959.

An extremely well-written and well-organized introductory book for children on the rise and decline of Mesozoic reptiles. The illustrations are awesome and excellent. A pronunciation list at the end of the book will help unprepared adults with the problems of pronunciation. Suitable for children of about age ten.

JAMES J. HILL

I LIKE BUTTERFLIES.

By Gladys Conklin; pictures by Barbara Latham. Holiday House, New York. $2.95. 26 pp.; ill. 1960.

Butterfies are irresistibly fascinating to children. *I Like Butterflies* contains color illustrations and brief textual descriptions of 19 butterflies and 7 moths—all common enough so that any child is likely to have the opportunity of seeing most of them. The attractive, simplified drawings clearly show their identifying colors and markings. This is primarily a picture book, and can be used as such for preschool children. It will also serve as a reading book for older children and as an introduction to identification and careful observation. The text does not include the names of all the insects pictured, but the page gives a complete list of the common names of all the butterflies and moths shown in the book.

MARY DEMEREC

OTUS. *The Story of a Screech Owl.*

By Robert M. McClung; illustrated by Lloyd Sanford. William Morrow & Company, New York. $2.50. 48 pp.; ill. 1959.

This is a welcome addition to the series of life-cycle stories by Robert M. McClung. The story of the screech owl, Otus, is sure to appeal to children of all ages. While it provides good "reading aloud" for a very young child, the large, clear, pleasant type will encourage a good reader in the third or fourth grade to enjoy it on his own. Older children, and even adults, may find much interesting and valuable information, not only about screech owls but also about other animals and plants that occupy the same habitats.

The animals of the story are not endowed with human emotions or human speech. Even the owl's name is that of the genus to which he belongs. The book's appeal rests on an interesting, concise presentation of sound scientific information. *Otus* could be used to great advantage in the nature study program of an elementary school. Excellent illustrations by Lloyd Sanford add to its value and charm.

MARY DEMEREC

THAT RASCAL, FRIDOLIN.

By Hans Fallada; illustrated by Imre Hofbauer. Pantheon Books, New York. $2.95. 157 pp.; ill. 1959.

This is the somewhat humorous story of the adventures of a badger. The book begins with a slow-moving fictionalized account of the life history of the badger, and moves, with the turning of the badger out of his den by a fox, to an exciting ending. The presentation shifts from the careful description of the life history into the drama of a narrative plot, and makes use, along the way, of motifs, names, and devices associated with the medieval beast tale. It is an entertaining book for children ten to fourteen, especially perhaps for girls, as the book was originally written by the author for his daughter.

JAMES. J. HILL

YOUR HEART *and How It Works.*
By Herbert S. Zim; illustrated by Gustav Schrotter. William Morrow & Company, New York. $2.50. 64 pp.; ill. 1959.

Most children are very much interested in the structure and functioning of their bodies, and the heart provokes more questions than any of the other organs. The first eight pages of this book answer the three questions most often asked by children: "How big is the heart?" "How much blood does it pump every minute?" "How much blood does a person have?"

The book presents many other interesting facts, discusses the evolution of the circulatory system, and includes clear diagrams of the circulatory systems of the various animal phyla. It also tells about some common heart ailments, and the methods used by modern medicine to discover and control them.

The brief explanations and simple, well-labeled diagrams make it possible for a teacher or a parent to find quick answers to children's questions; the large, attractive type is sure to tempt children to seek the answers for themselves. The subject matter covered is usually found in eight- and ninth-grade general science textbooks, but the simplicity and clearness of Herbert Zim's presentation bring the information within the reach of much younger children.

MARY DEMEREC

WORDS OF SCIENCE *and the History Behind Them.*
By Isaac Asimov; illustrated by William Barss. Houghton Mifflin Company, Boston. $5.00. vi + 266 pp.; ill. 1959.

The author's introduction states: "Far from frightening people away from science the scientific vocabulary . . . should be one of the most powerful attractions in science." His book attempts to convert the reader to this point of view.

The book consists of 250 one-page explanations, each defining a word chosen by the author from the field of biology, astronomy, physics, chemistry, technology, or geology. Some of these belong to classical terminology, some are of recent origin, and a few are words in common usage ("grammar," "almanac," etc.). Each discussion gives the word's meaning, its historic background and derivation, and other interesting information. Since all the explanations involve additional scientific terms, which are treated in the same way, the index lists approximately 1200 words about which such information is available.

The book is interestingly written, and can be used to advantage by junior and senior high school students as a reference book in science courses or as an aid in understanding news items that report new scientific developments.

A book of this size obviously can define only a limited number of terms. Its purpose is to teach a creative, analytical approach to the learning of the scientific language.

MARY DEMEREC

DOCTOR PARACELSUS.
By Sidney Rosen; illustrated by Rafaello Busoni. Little, Brown & Company, Boston and Toronto. $3.50. viii + 214 pp.; ill. 1959.

Doctor Paracelsus is a story written for youngsters, a story whose subject is perhaps as much *enthusiasm* as *science*. A highly fictionalized biography of Paracelsus, it presents a running tale of the lifelong experiences of a courageous wonderer dedicated to the improvement of medicine through alchemy. It expends considerable effort to portray the life and history of the times. Perhaps a child should review the book, since only a child could say how far the author has succeeded in indicating what it felt like to be an iconoclastic scientist in the 16th century; to this jaded and ancient reviewer it would seem that Rosen has done it well. The line drawings that illustrate the text are delightful, and alone are worth the modest price of the book. A short bibliography and short index are included.

JANE OPPENHEIMER

ECOLOGY AND NATURAL HISTORY

RECHERCHES PHYTOGÉOGRAPHIQUES SUR L'ÉTAGE DE VÉGÉTATION MÉDITERRANÉEN ARIDE (SOUS-ÉTAGE CHAUD) AU MAROC OCCIDENTAL. *Trav. Inst. sci. Cherifien, Ser. Bot., No. 13.*
By R. Nègre. Société des Sciences Naturelles et Physiques du Maroc, Rabat. 1,840 fr. (paper). iv. + 385 pp. + 4 pl.; text ill. 1959.

To gain a quick notion (in English) of Morocco today and its vegetation, one should read Marvin

Mikesell's excellent study of one section of this "plundered planet" published in *Science* for August 19, 1960. Then, to gain a detailed knowledge of Morocco's plant life (in French), see Negre's monograph, presented in somewhat different form as a doctoral thesis at the University of Montpellier. His study is a comprehensive analysis based on ten years of field study and extensive reading on desert ecology; 153 references are *cited* in his account, 17 of them being his own published in the last decade. There are 6 principal chapters: geomorphology, geobotany, biology of species, climatic and edaphic interpretations, the composition of the vegetation units, and general conclusions. There are also 6 appendices, the gazetteer itself will assist all biologists concerned with Morocco maps, and there are 16 well-chosen photographs illustrating the vegetation, as well as many textual charts and diagrams.

Negre's study focuses on a sector of the larger screen illuminated by Louis Emberger's regional study of the plant life of arid Mediterranean Africa. The plant associations identified are based on soil characteristics, calcareous soils forming by far the largest component. Species influenced by more or less constantly available water supplies, either stagnant or running, and nitrophilous and rock-inhabiting species, all are classified in separate categories from the edaphic groups. The real scarcity of individual plants is notable. Behind this monograph are the days and nights in desert travel, with the discomforts of winds, insects, and withering heat, that remain unrecorded.

By way of postscript it may be noted that the three plant families represented in greatest numbers are the pea, lily, and pink families. The floristic contrast with our own Southwestern deserts again emphasizes the unlikeness of the two arid regions.

JOSEPH EWAN

BIOLOGIE DES EAUX SOUTERRAINES LITTORALES ET CONTINENTALES.

By Claude Delamare Deboutteville. Hermann et Cie., Paris. 60 NF. 740 pp.; ill. 1960.

An unusual and fundamental phase of animal ecology which has been largely neglected in the United States deals with the populations of organisms inhabiting interstitial waters of marine and freshwater sandy beaches, as well as those found in phreatic waters below river beds and elsewhere in permeable subterranean gravel and coarse sand deposits, sometimes miles from open water. This volume is essentially a summary and review of the more than 700 papers which have appeared on this subject, especially since 1940 and especially in European journals. The author is unquestionably the outstanding authority on the subject.

Interstitial communities sometimes extend to a depth of several meters in suitable substrates. They are often remarkably dense and usually contain familiar protozoans, but the great majority of micrometazoans are peculiar to this habitat and occur nowhere else. The early chapters of the volume are devoted to collection methods, physical and chemical conditions in the wet sand and gravel, as well as morphological, reproductive, and physiological adaptations of the fauna. Later chapters discuss the general ecology and taxonomy of such typical interstitial groups as Polychaeta, Archiannelida, Oligchaeta, Rotatoria, Gastrotricha, Nematoda, Echinodera, Turbellaria, Nemertea, Tardigrada, Acarina, and a host of crustaceans, including Mystacocarida, Ostracoda, Copepoda, Syncarida, Thermosbaenacea, Isopoda, and Amphipoda.

Chapters XV to XXII form a series of major taxonomic and regional ecological contributions, including such topics as: microisopods of sandy beaches, the ecology of *Derocheilocaris remanei*, and the marine beach interstitial faunas of Algeria, Tunisia, and Italy. Closing chapters are devoted to problems of migration, speciation, and zoogeography. Six of the 26 chapters are reprints of articles appearing recently in *Vie et Milieu*.

Invertebrate zoologists and ecologists will derive much interest and stimulation from this stout volume.

ROBERT W. PENNAK

ECOLOGY OF THE PEREGRINE AND GYRFALCON POPULATIONS IN ALASKA. *Univ. Calif. Publ. Zool., Vol. 63, No. 3.*

By Tom J. Cade. University of California Press, Berkeley and Los Angeles. $2.50 (paper). iv + pp. 151–267 + pl. 17–26; text ill. 1960.

These two large species of raptorial birds were studied over a period of years in an environment that is geologically young and biologically relatively simple, in an effort to elucidate their mutual interactions. It was found that in maritime situations the two were not strictly sympatric and have achieved ecological equivalence, but in more rugged country there was competition for nesting sites on cliffs, and, in some areas, some competition for food as well. Its greater size and strength, and its earlier breeding cycle, which gives it a certain priority in nesting sites, gives the advantage to the gyrfalcon. On the other hand, the peregrine is numerically the more successful species, because of its annual escape from the rigorous arctic winter by migration, its greater adaptability to various kinds of nesting sites (it is less restricted to cliffs than the gyrfalcon), and because of its summer exploitation of a more constantly adequate food supply.

Studies of this sort demand detailed reporting of the basic data, for it is only by considering and scrutinizing them closely that it is possible to judge

the validity of the conclusions. Cade's deductions from his evidence seem sound and valid.

HERBERT FRIEDMANN

THE KING PENGUIN *Aptenodytes patagonica* OF SOUTH GEORGIA. *1. Breeding Behaviour and Development. Falkland Islands Dependencies Survey. Scientific Reports No. 23.*

By Bernard Stonehouse. Her Majesty's Stationery Office, London. £1 5s. Od. (paper). ii + 81 pp. + 7 pl.; text ill. 1960.

THE ECOLOGY AND TAXONOMY OF SOME ANGOLA BIRDS. *(Based on a Collection made in 1957). Bull. Brit. Mus. (Nat. Hist.) Zool., Vol. 6, No. 7.*

By B. P. Hall. The British Museum (Natural History), London. 40s. (paper). ii + pp. 369–453 + pl. 5–6; text ill. 1960.

WALVISSEN.

By E. J. Slijper. D. B. Centen's Uitgeversmaatschappij, Amsterdam. Fl. 32.50. 524 pp.; ill. 1958.

The author here treats the subject of whales exhaustively in a style that is designed for the well-educated layman. Technical terms are avoided, although almost all that is known about whales is authoritatively set forth. The anatomy, physiology, pathology, ecology, and behavior of all types of whales are discussed, as are the many problems of modern whaling. Many illustrations are of quite high quality. The book deserves to be issued in an English translation so that it may reach the wide audience for which it was designed.

M. L. WOLBARSHT

RIVER POLLUTION. *1: Chemical Analysis.*

By Louis Klein. Academic Press, New York; Butterworth Scientific Publications, London. $6.00. x + 206 pp. 1959.

Louis Klein's current book extends the analytical sections of his earlier *Aspects of River Pollution* into a technical reference work that will be outstandingly useful to the laboratory and field chemist and waste engineer. It is the effort of a single, experienced, and capable chemical specialist. It has a critical clarity and coherence that is not found in any of the popular official and standard manuals of water and waste analysis.

The organization of the discussions makes the book particularly valuable to the active research man and analyst as a quick reference and summary; the sections are topically developed and indexed for rapid survey. Individual analytical techniques are described briefly, with short statements giving the principles, indicated applications and limitations, sensitivity ranges, precision, and interfering conditions. Approximately 600 pertinent papers are organized and reviewed in the 11 major chapters of the book.

The book will be most valuable to the active waste control worker, but officials and administrators will find the remarks on effects of special wastes upon water quality, and the extended final chapter on the significance and interpretation of tests, most useful.

Tables of data, largely from British experience, are used to demonstrate typical waste water properties and the effects of wastes upon natural waters. Useful equations and formulas have been thoughtfully included at appropriate spots in the text and a number of conversion tables appear in an appendix.

The characteristics and analytical techniques for a large number of waste classes and compounds are described in this book. These include the readily oxidizable and fermentable organic, nitrogenous, and sulfur groups, toxic metals, and specialized organic compounds including recent insecticides and detergent materials. The basic chemistry and physics of the conventional water quality measurements and of British sanitary practice are given. Essentially, Klein has prepared a series of tightly written short monographs and has packed these into 200 pages. He has presented an excellent argument for the technical specialist in water resources.

CHARLES E. RENN

EVOLUTION

DIE EVOLUTION DER ORGANISMEN. *Ergebnisse und Probleme der Abstammungslehre. Second Edition, Part 6.*

Edited by Gerhard Heberer. Gustav Fischer Verlag, Stuttgart. DM 19.80 (paper). iv + pp. 1109–1326; ill. 1959.

The issue of the sixth *Lieferung* completes publication of the second revised edition of this great compendium, organized for assembly into four parts in two volumes. The last three articles are here presented, along with author and subject indexes and front matter for the whole work. The first edition was published during the war (in 1943) and went out of print within a few months, so that it remained almost unknown outside of Germany. The enlarged and almost completely revised second edition, published at intervals from 1954 to 1959, is more readily available. With its 1242 pages of text, 83 pages of indexes, and 418 illustrations, it is the most modern and most complete treatment of many aspects of evolution available in any language. It is inevitable that some contributions are weak and some subjects (notably paleontology) are inadequately covered, but it is on the whole an exceptionally valuable compilation, and the editor, Gerhard

Heberer, is to be warmly congratulated on its completion.

The previous *Lieferungen* have already been reviewed (*J.R.B.*, 31: 44.1956 and 33: 148.1958). The present articles, completing the section on hominid phylogeny, are: Heberer on the subhuman phyletic origin of man, Reche and Lehmann on the genetics of human race formation, and von Eickstedt on the phylogeny of the psyche, or paleopsychology.

Heberer's chapter barely mentions the early Tertiary primates or the australopithecines. (The latter were treated at somewhat greater length along with the fossil Hominidae in a previous chapter by Geiseler). This contribution is a summary but adequate review of the Miocene and Pliocene Pongidae, somewhat artificially grouped as Dryopithecinae. Heberer would derive the Hominidae from an arboreal but not specialized brachiating pongidlike Miocene anthropoid. His well-known view that *Oreopithecus* is a hominid, although not directly ancestral to *Homo*, is here repeated. Discovery of a skeleton of *Oreopithecus* was too late for more than bare mention in a footnote.

Reche and Lehmann take the reasonable view that human races are in most respects like those (or, better, like the subspecies) of other animals, developed by the same kind of interplay of mutation, isolation, population changes, genetic drift, hybridization, and selection. The major races are seen as evolving allopatrically and for the most part by selective adaptation to climatic conditions. The authors do, however, consider other evolutionary factors as important in particular instances, notably genetic drift as (somewhat equivocally) documented in Australian aborigines by Birdsell, whose work is reviewed at some length.

The impression may reflect only my own incompetence in genetical and comparative psychology, but I do suspect that von Eickstedt's contribution will be uncongenial, in part even incomprehensible, to many who are competent in that field. The approach is strongly aprioristic and deductive on principles that seem to me to have little or no evidential basis. Correspondence of ontogeny and phylogeny is taken as established and fundamental. For example, the preschool child, ages five to six, is precisely equated with the psychogenetic level of *Pithecanthropus*. This chapter is an unsatisfactory ending for what is in most respects so excellent a work.

G. G. Simpson

Evolution by Natural Selection.

By Charles Darwin and Alfred Russel Wallace; foreword by Sir Gavin de Beer. Published for the XV International Congress of Zoology and the Linnean Society of London by the Cambridge University Press, Cambridge and New York. $4.75. viii + 288 pp. 1958.

This republication of some classics in the development of the theory of evolution by means of natural selection represents a highly fitting commemoration of the Darwin centennial year. Besides an extended Foreword by Sir Gavin de Beer, the book contains as preliminary matter the Introduction written by Sir Francis Darwin in 1909 for Charles Darwin's *Sketch* of 1842 and his *Essay* of 1844. The bulk of the volume consists of the *Sketch* and the *Essay*, and of the two papers, by Charles Darwin and Alfred Russel Wallace respectively, presented to the Linnean Society on July 1, 1858. For good measure, a letter from Darwin to Asa Gray, dated September 5, 1857, is printed as further evidence of the stage of development of Darwin's ideas in the years before the publication of the *Origin*. Everyone interested in the history of science, and in the development of evolutionary ideas in particular, will prize this addition to his library. It is as indispensable as the *Origin of Species* itself. Of all its contents, the *Essay* of 1844 is clearly the most substantial, even if of less historical importance than the jointly presented papers of 1858. In the *Essay*, Charles Darwin developed his ideas almost as fully as, and in some respects presented them better than, in the *Origin of Species* itself. Again one wonders: are there any modern scientists at all who would devote 15 years to the further gestation of a theory already so fully and satisfactorily worked out? Would the publication of the *Essay*, in 1844, have failed to convince the scientific world of the theory's validity? Was Darwin justified in his long wait? We can never answer these questions positively. At any rate, it is most pleasing to have so available, in the Cambridge University Press' customary fine format, the stages in the gestation and birth of the *Origin*.

Bentley Glass

Natural Selection and Heredity.

By P. M. Sheppard. Hutchinson University Library, London; Philosophical Library, New York. 10s. 6d., $6.00. 212 pp.; ill. 1958.

This readable little volume, surprisingly inclusive for its size, approaches the subject of natural selection simply enough for those with no previous knowledge of the field. It presents many basic concepts such as dominance as an attribute of the phenotype and the importance of a balanced integrated system of genes, "the gene complex," to cite only a couple. While it does not deal comprehensively with its broad range of topics (from simple Mendelian principles to polygenic inheritance and the evolution of dominance, polymorphism, recombination, mutation,

genetic drift, ecological genetics, and the origin of species), nevertheless these are approached skilfully enough to stimulate reference to the original papers.

There is possibly some oversimplification in the emphasis on the particulate nature of inheritance and "genes which are discrete bodies." A few terms are used loosely; e.g., "sex controlled" inheritance is distinguished from sex-linkage but equated to "sex-limited" inheritance, only to be followed by the example of premature baldness in man—an example used by Snyder and David to illustrate "sex-influenced" as *contrasted* to "sex-limited" traits, and one that is highly controversial at best.

On the other hand, the chapters on polymorphism, with classical examples of transient polymorphism (e.g., industrial melanism) and of stable polymorphism maintained through heterozygote advantage, are very lucid. Moreover, obvious but fundamental factors often omitted in elementary texts or neglected in more advanced volumes are incorporated. To quote: "It will be remembered that genes controlling different characters are found together in the same chromosome. Therefore, if a particular character is being selected in an experiment not only will new combinations of polygenes affecting this character be selected but also allelomorphs at other loci, affecting different characters, which happen to lie between them on the chromosome.... Thus integrated polygenic systems result in an 'inertia' which has to be overcome by large and prolonged environmental change...."

While the discussion of polygenic inheritance may not follow Mather's views to the letter, it is commendable that the term polygenes is associated with Mather's extensive investigations and *not misused* as a loose synonym for multiple factors, as is all too commonly done by other authors.

The inclusion of Dobzhansky's astute observation, "that it is meaningless to ask the question: which is more important, drift or selection, in causing evolution under a given set of circumstances . . .there will be an interplay between these forces," presents a familiar point but one well made. Perhaps this concept and that of genetic homeostatic mechanisms could have received more emphasis or at least some reference in the conclusion. Despite these few and minor criticisms, *Natural Selection and Heredity* is timely, well written, and documented and is to be recommended as pleasant reading for biologists and nonscientists alike.

It might be noted that the discrepancy in British and American prices (10s. 6d. and $6.00) is rather considerable. While the type, Times New Roman face, is exceedingly legible, one might willingly be satisfied with a somewhat less expensive binding and type for so small a volume.

BERNICE COHN

PERMIAN GASTROPODA OF THE SOUTHWESTERN UNITED STATES. *Pleurotomariacea: Portlockiellidae, Phymatopleuridae, and Eotomaridae. Bull. Amer. Mus. Nat. Hist., Vol. 114, Art. 2.*

By Roger Lyman Batten. American Museum of Natural History, New York. $3.00. Pp. 157–246 + pl. 32–42; text ill. 1958.

This work is confined to a rather primitive group of gastropods, the Zygobranchia of the classical taxonomists. The student of recent mollusca whose knowledge of paleontology does not extend backward beyond the Tertiary is likely to be astonished by the large number of genera that flourished in the Permian, and which became extinct at the end of that period, to be succeeded by heterobranchiate forms bearing but little resemblance to the fauna which they displaced.

It is interesting to speculate as to just what did happen at the end of the Permian Period. Up to this time many, perhaps most, gastropod shells were spirally coiled but with no evidence of a helical element, i.e., there was nothing corresponding to the dextral and sinistral types of coiling that eventually came to prevail over the more primitive discoid type. When helical coiling did arise, partly as the result of embryonic torsion, although not entirely so, did it come about as the result of a small beginning and a single line of descent that eventually produced the great multiplicity of forms that we know today? Or did all the Permian gastropods adopt helical coiling at about the same time so that there were many lines of parallel descent? Evidence seems to favor the latter possibility, strange as it may seem, but it is too soon to frame any hypotheses. What would we not give to find in some isolated region a population of surviving Permian mollusca! The recent discovery of two living species of Tryblidiacea, formerly known only from the Cambrian, makes this hope seem less unreasonable than it would have appeared a few years ago. In the meantime, treatises such as the present ones are to be welcomed, for they increase and disseminate knowledge as to what the molluscan world was like "before the mountains were brought forth or ever the earth or the world were made."

JOSHUA L. BAILY, JR.

THE VERTEBRATE FAUNA OF THE SELMA FORMATION OF ALABAMA. *Part V. An Advanced Cheloniid Sea Turtle. Part VI. The Dinosaurs. Fieldiana, Geol. Mem., Vol. 3, Nos. 5 and 6.*

Pt. V by Rainer Zangerl; Pt. VI by Wann Langston, Jr. Chicago Natural History Museum, Chicago. $3.50 (paper). iv + pp. 281–361 + pl. 30–34; text ill. 1960.

AN ANALYSIS OF INTRASPECIFIC VARIATION IN THE KANGAROO RAT *Dipodomys Merriami. Univ. Calif.*

Publ. Zool., Vol. 67, No. 2.

By William Z. Lidicker, Jr. University of California Press, Berkeley and Los Angeles. $2.00 (paper). iv + pp. 125–212 + pl. 9–12; text ill. 1960.

GENETICS AND CYTOLOGY

INTRODUCTION TO QUANTITATIVE GENETICS.

By D. S. Falconer. The Ronald Press Company, New York. $6.00. x + 365 pp.; ill. 1960.

Prior to the appearance of Falconer's book, quantitative genetics, as important as it is in both theory and practice, has never been treated systematically and clearly in a way comparable to that of Mendelian genetics. Previous books on this subject are either limited to one aspect of the problem (such as the analysis of F_2, F_3, and backcross data) or profuse with elaborate mathematical deductions (such as the breakdown of genetic variance into an infinite number of components, while the presently available experimental data are hardly sufficient to determine more than a few of them with any accuracy at all). Likewise, research reports are not infrequently either a compilation of numerical tables without any reasonably consistent interpretation or a purely mathematical or deductive treatise without observational substantiation. Falconer has tried successfully to strike a balance between theory and fact.

The study of quantitative genetics requires a certain amount of acquaintance with statistical techniques, of course. But I do not see why this should prevent students and biologists from gaining some real understanding of the principles involved in quantitative inheritance, as most students in biology and agriculture have had at least that much training in statistics. One of the roadblocks may be the way in which these principles are presented. For instance, the fundamental theorems in correlations between relatives were worked out in 1918, have been appreciated by only a few biometricians, and have remained unknown to general students for many years. If properly presented, anyone who has learned about linear regression from an elementary statistics course will have no difficulty in understanding the subdivision of genetic variance and the correlation between relatives. Falconer treats the subject from first principles and proceeds logically from one topic to another. The book is well organized, and not a mere compilation of miscellaneous formulas or a mere review of experimental results.

The book consists of 20 chapters which can be grouped into four sections: Gene Frequency and its Changes; Metric Characters and Selection; Inbreeding and Crossbreeding; and, Some Special Topics.

One may criticize the book as being too elementary and as not helpful for research workers. As to the first point, I think that an elementary over-all introduction to quantitative genetics is just what we need at the present time. As to the second point, possibly with the exception of a few biometricians, most experimenters can benefit from the book, without having to agree with everything in it. This is the *first* book to be recommended to those who want to know what quantitative genetics is.

C. C. LI

PROBLÈMES D'ULTRASTRUCTURES ET DE FONCTIONS NUCLÉAIRES. *Exposés Actuels de Biologie Cellulaire. Edited by J. André Thomas. Masson & Cie., Paris.* 42 NF (paper). xx + 222 pp.; ill. 1959.

Five representative French and Belgian scientists and one from the United States were selected by the distinguished editor at the Sorbonne, J. André Thomas, to contribute to this fifth volume of the *Biocytologia* series. It is good that the title includes the word *problems*, because in spite of the well-written reviews, each author deplores the lack of definitive answers.

In the first chapter, a valuable bibliography of 188 papers on the ultrastructure and function of the nuclear membrane is annotated and discussed by C. A. Baud. This chapter relies heavily on electronmicroscopy, and dismisses most of the work on freshly isolated nuclei and on living cells. Problems of "pores" and texture and perinuclear attachments of cytoplasm are thoughtfully presented with the aid of theoretical diagrams. Transfers of material across the membrane are now among commonplace observations.

Chapter Two, La Physiologie du Nucleole, was compiled by A. Ficq of Brussels. Her wide experiences in radioautography have led her to conclude, along with many others, that nucleoli consist largely of RNA and protein. Excellent evidence is offered for the tremendous role of nucleolar RNA in protoplasmic syntheses of protein. It is unfortunate that the author neglects the fact brought out in Grassé's later chapter that osmic vapor, so widely used in electron microscopy, produces deep alkalosis of the nuclear contents, and thus disintegrates chromosome structure and destroys nucleolar integrity. Ficq's final words for the genetic and metabolic roles of the nucleolus are, "still obscure."

H. Lenormant and P. Grassé of Paris have collaborated on an extensive review of the physical state of DNA-proteins. So much has been written elsewhere on this subject and on the socalled ultrastructure of chromosomes that it is hardly surprising that the general reader will find little that is new. It is of interest that even in 1959 these critical authors state that it is not yet known how chromosomes

can be fixed correctly. Attempts to correlate X-ray diffraction patterns with genetic information and electron microscopy seem to have lagged at least five years behind in cellular physiology.

A long chapter by J. P. Faure, on chemical extractions of nucleic acids, is of considerable value to technologists. It contains some 300 references, chiefly to the literature of the subject in the United States. Attention should be drawn to the wide acceptance in Europe of the term *Infective DNA*, especially that extracted from viruses, because it is certain that this concept will become widely employed in the experimental cancer literature.

A. D. Glinos, of the Walter Reed Army Medical Center, contributes an excellent short review of cytoplasmic influence on the nucleus during growth. One might ask for an equal consideration of the conversely directed influence. Glinos offers some of his own data on the stimulatory effect of partial exsanguination upon mitosis. As the editor points out, homeostatic control of regeneration has long been this author's particular specialty. Glinos concludes with theoretical considerations and speculations on the biochemistry of DNA and RNA.

One feels that the volume as a whole is an admirable review of a difficult subject. Nevertheless, it seems to rely too heavily on hypotheses and hopes, while neglecting other, more solid findings. The book contributes to basic knowledge, but it leaves a rather vague impression of scholarly bewilderment.

WILLIAM R. DURYEE

RADIOBIOLOGY AT THE INTRA-CELLULAR LEVEL. *Proceedings of a Conference held at Catalina Island, Sept. 9–12, 1957. First U. C. L. A. Conference on Radiobiology.*

Edited by T. G. Hennessy, B. H. Levedahl, L. S. Myers, Jr., et al. Pergamon Press, New York, London, Paris, and Los Angeles. $8.50. x + 208 pp.; ill. 1959.

Various terminal aspects of radiobiological change are known with a good deal of certainty, and literature on the subject continues to increase steadily in volume. These changes, which include mutations, chromosomal alterations, cell death, biochemical and morphological variations, and aging, are subject to pre- and post-irradiation modification, and give rise to the hope that the primary events which result from the introduction of radiant energy into the cell and which through amplification become grossly manifest may be isolated, identified, and understood. The radiobiologists know how elusive these answers are likely to be, and indeed how perplexing is the wealth of data already accumulated and from which generalizations are made. This volume, which attempts to deal generally with the broad problem of intracellular change induced by radiation, reflects these inherent difficulties, not only in the interpretation of available data but also in asking of the cell the proper questions to be answered in the future. It is difficult even to know from what experimental direction elucidating information is likely to come, although a more recent symposium, held in Puerto Rico in February, 1960, suggests that radiation events at the physical and physical-chemical levels, and taking place prior to 10^{-6} seconds after the introduction of radiation, must be understood before we can hope to visualize how radiological change at the molecular level can be amplified into such gross effects as a broken chromosome or a killed cell. Clearly, a whole chain of events takes place: physical events (absorption of energy and its movements in molecular structures) → physical-chemical events (active radicals and activated molecules and their interplay with biologically important sites) → chemical events (oxygen involvement, for example) → biological events (metabolic determination of magnitude of change) → end result. The first three steps occur in 10^{-15} to 10^{-6} seconds, and are detectable only by strictly physical means; the end result may occur minutes, hours, days, or even years afterward. The biological gap in our chain of events is a veritable Grand Canyon of ignorance.

The present volume, however, provides a mass of information of varying sorts and degrees of complexity on radiosensitivity, sensitive sites, recovery, and cellular interactions. Like most symposia without prepared and submitted papers, the discussions leave something to be desired. They are somewhat disorganized, rambling, often irrelevant, not very closely edited, and frequently cryptic, since reference is to figures which are not included. The index is of little aid in following through a given topic, and the small, compact print accorded the discussions (as contrasted with the large print for the opening exploratory speech of each session) makes reading difficult and sometimes annoying. The volume is consequently a book for the active radiobiologist, and not at all a volume one can recommend to anyone outside this specialized field.

C. P. SWANSON

CYTOLOGY AND EVOLUTION.

By E. N. Willmer. Academic Press, New York and London. $10.00. x + 430 pp.; ill. 1960.

In his Preface the author states that this is an unusual book. One can, of course, accord him the usual courtesy of agreement, but in this instance one should also applaud him for having given to cytology another dimension, or perhaps more accurately, another direction for profitable exploration.

No other book on cytology of which I am aware presents the subject matter of cells in quite this manner. Cytology and evolution have, to be sure, been

intimately linked before. The science of genetics has made this inevitable, and cytogenetics is used as a term to designate this area of knowledge. C. D. Darlington and M. J. D. White have been the most active expositors in this field, and their major emphasis has been on the hereditary apparatus of the cell, that is, on the chromosomes and their structure and behavior.

Willmer mentions chromosomes only incidentally, and devotes his attention to the evolution of cell types, achieving thereby "a tentative genealogical tree of the families of cells of an organism . . . as a key to the manner in which cells differentiate and to the manner in which they behave in tissue culture." Tissue culture studies, with the environment under more or less rigid control, have suggested that a variety of cells tend to resolve themselves into three main groups—mechanocytes, epitheliocytes, and amoebocytes—having peculiarities of pattern, contact, biochemistry, locomotion, and sensitivities. With this in mind, the author goes back to the protozoan cell and its problems of maintenance in a changing environment, and thence to multicellularity and its problems of cell contact, form, diversity, differentiation, gradients, polarity, and cellular environments. Out of these considerations emerges a concept of evolutionary cytology which integrates a substantial amount of information from cytology proper, histology, comparative biochemistry, and cell physiology. The author has not hesitated to interpret and to speculate with courage and audacity when the circumstances of information warrant, but when he has done so it is not with a sense of finality, but rather with a sense of ordered adventure and of optimism for the future.

Whether, in his thoughts and in his writing, Willmer has so arranged his material as to give a correct phylogenetic sequence of cell types is relatively unimportant at the moment. Time will bear him out or discard his speculations. He has, however, given us food for thought, suggestions for experimentation, and data upon which we can speculate ourselves. This is reason enough for a book.

C. P. Swanson

GENERAL AND SYSTEMATIC BOTANY

A California Flora.

By Philip A. Munz; in collaboration with David D. Keck. Published for the Rancho Santa Ana Botanic Garden by the University of California Press, Berkeley and Los Angeles. $11.50. viii + 1681 pp. + 1 pl.; text ill. 1959.

California's first flora was the two-volume *Bot. Cal.* (1876–1880) which still makes fascinating browsing. Jepson's *Manual* epitomized the intervening half-century, and now Munz updates our knowledge. The present volume matches Fernald's *Manual* in size, and both together represent our latest comprehensive summaries which will be used by the two great centers of population in this country. Genera not previously listed in any California manual include *Benitoa, Tracyina, Legenere, Dimeresia, Sympetaleia, Stylomecon, Matalea,* etc. The most exciting discovery since Jepson's *Manual* is perhaps the new grass genus *Ectosperma* which was brought to light in Inyo County by Misses Alexander and Kellogg. On the other side, some plants have evidently already become extinct, a few before we even learned their chromosome numbers: *Arctomecon merriami, Potentilla multijuga, Holocarpha macradenia, Agave shawii, Stemodia durantifolia,* and perhaps others. Munz's *California Flora* will be the manual for the professional botanist for years to come, but Jepson's *Manual* will probably remain the favorite for the beginner, since its drawings and general format carry an appeal that this latest, corrected, and most complete product cannot match, despite the hundreds of errors, mostly bibliographic, that fleck the pages of Jepson's *Manual* and have been corrected in Munz's *Flora.*

Munz's taxonomic treatments are in general conservative at the generic level. For example, *Sequoiadendron* is taken up, but the segregate *Heyderia* is not. *Diplacus* is merged with *Mimulus,* and *Euphorbia* includes what may be three genera. *Dudleya* embraces *Stylophyllum* and *Hasseanthus,* which have recently been reduced on cytogenetic evidence, although admitted as genera by both Jepson and Abrams. Munz admits *Ivesia, Horkelia,* and *Potentilla,* however, when the base number of $2n = 28$ occurs in all three genera, a criterion which in other instances would decide their congeneric status. Both subspecies and varietal names are accepted side by side in the treatment of genera with some resulting confusion. *Mimulus primuloides* var. *pilosellus* stands beside subsp. *linearifolius* with scant significance in an evolutionary sense. An excellent feature is the citing of chromosome numbers from readily available data, although no protracted search has been made to locate such data, and the absence of a number for a species must not be taken as signifying that its cytology is unknown. The responsible author of the chromosome data is cited—a space-consuming matter; Clapham, Tutin, and Warburg, in dealing with the British flora, did not see the necessity of citing authors for chromosome data but gave alternative figures with a question mark following the less reliable genom.

The reader acquainted with the California flora will raise his own queries as he consults the *Flora.* Here are some of mine: *Eupatorium adenophorum* is sometimes surely a feral plant independent of man's hand, as when encountered in the coastal canyons of

the Santa Lucia Mts.; the presence of *Adenocaulon* in the Tehachapi Mts. of Kern County, overlooked there by Munz (but cf. *Bull. S. Calif. Acad. Sci.*, 29: 98), must be a Pliocene relict that once was associated there with *Lyonothamnus*; the curious fern *Asplenium septentrionale*, omitted from the *Flora* (but cf. *Amer. Fern. J.*, 35: 29), must be, on the other hand, an arcto-Tertiary survivor; Fernald's scheme for entering introduced elements in the flora by contrasting type face is highly desirable, serving as it does to preserve the aboriginal content of the state's flora apart from immigrants, thus *Salvia grahami*, picked up as long ago as 1909 along the Sur River, assumes its proper perspective for what it is, a waif that has failed to persist in the wild where other *Salvias* are successful species; is not *Stemodia erecta* (Browne) Minod the valid name for *S. durantifolia*? doesn't *Kelloggia* exhibit two forms, a pubescent and a glabrous form, which merit recognition? would it not be useful to anticipate *Stegnosperma halimifolia*, taken in Baja, California close to the state line, as a California species by inserting it beneath a short rule in its taxonomic position?

It may be well at this point to recall Bradley Patten's words when introducing one of his embryological works, to the effect that it "is inevitable in any field where our knowledge is growing rapidly [that] there is much difference of opinion as to the significance of certain of the observed facts." This in no wise diminishes the honor due the achievement!

To repeat what was said of Munz's 1935 *Manual of Southern California Botany*, that "no systematic botanist or botanical library should be without this book," would be superfluous. Buy it, use it, annotate it, forward your additions and corrections, toward that next epitome of one of the richest, most diversified floras of the world. It is of interest to note the increment of knowledge since *Bot. Cal.* (1876) for four genera taken at random against Munz's *Flora*: *Senecio*, 17 vs. 38 species; *Eryngium*, 1 (with a var.) vs. 7 species; *Trifolium*, 26 vs. 49 species with many subspp.; *Astragalus*, 48 vs. 93 species with many subspp. What will the next century bring?

JOSEPH EWAN

MARINE ALGAE OF THE EASTERN TROPICAL AND SUBTROPICAL COASTS OF THE AMERICAS.

By William Randolph Taylor. The University of Michigan Press, Ann Arbor. $19.50. xii + 870 pp. + 80 pl.; text ill. 1960.

Rarely could it be said with more accuracy that here is the man to do the job. William Randolph Taylor is undoubtedly the world's expert on the marine algae of the North American coast. He has traveled extensively and familiarized himself with more distant flora, both fresh and in herbaria; and he has collected, photographed, studied, and lectured on algae for many years. This book, begun nearly thirty years ago, represents his patient and detailed study of America's tropical algae, their taxonomy, their distribution, and the history of their literature.

Marine Algae of the Eastern Tropical and Subtropical Coasts of the Americas is written for the practicing taxonomist. It largely retains the systematic arrangement of Fritsch and Kylin, and omits the mass of information now available on life histories of algae. The need for such a book is apparent. There is no manual of algae covering the territory from North Carolina and the Bermudas to Brazil, nor, in most areas, is there even a check list of the local algae.

Biologists already familiar with Taylor's *Marine Algae of the Northeastern Coast of North America* will recognize a parallel organization in the present manual. Again, only macroscopic marine algae are represented. Keys to families, genera, and species are provided. Each species is characterized morphologically and ecologically, and reports of its occurrence, plus references, are listed. A great number of the species are represented by one or more drawings or photographs which ably supplement the text.

Taylor has provided a very useful introductory chapter which discusses the history, geographical distribution, habitats, collection, and preservation of tropical algae. According to this, nearly 30 per cent of the species listed are cosmopolitan, and relatively few of the others—Taylor suggests about 28 per cent—are restricted to the Caribbean area. Compared to the 401 species of marine algae of the northeastern Atlantic coast, Taylor's tropical and subtropical list includes 760 species.

Probably the greatest labor involved in preparing this manual was the tedious checking of each species record to determine its validity. In a large genus such as *Cladophora* this results in the acceptance of 35 species, and the rejection of more than 40, for each of which a reference is provided. Although the author suggests that previous collecting in the Caribbean area has been relatively sparse, his own careful checking of uncertain records and comparison of herbarium specimens have left him with only 8 new species and 4 new varieties to record in this book.

Two minor but useful features, present in his other manual, are missing from this work of Taylor's: a complete systematic check list, and a key to the orders. An even more valuable inclusion might have been a map of the area described. On the other hand, the author has published for the first time several of his own underwater photographs of algae, which are among the most interesting illustrations of the present volume. These, in addition to the superb drawings done by the author and various coworkers, can hardly be praised enough, both for their value and for their beauty. Phycologists, ecologists, taxonomists, and all biologists of tropical American seas

will appreciate this scholarly and practical manual of marine algae.

ANNETTE W. COLEMAN

PLANT PHYSIOLOGY

PLANT GROWTH SUBSTANCES. *Second Edition. Plant Science Monographs.*

By L. J. Audus. Leonard Hill (Books), London; Interscience Publishers, New York. $10.00. xxii + 554 pp. + 34 pl.; text ill. 1959.

Some areas of biology tend to expand horizontally, at least for a time, adding new facts and new observations without penetrating very deeply into the understanding of principles, while other areas may undergo extension in depth, gaining insight into principles and major patterns of action without working out in detail their application in more than a very few systems. If biochemical genetics is thought of as an example of the latter type, the field of plant growth substances is a good specimen of the former—for in the years since Audus wrote the first edition of this book (*Q.R.B.*, 29: 68. 1954) a vast amount of new information has been added, while the key questions have remained almost wholly unanswered.

That the precise mechanism of action of the auxins in controlling the growth of plants should be still unknown is, of course, not surprising, since no student of hormone action in *any* organism can lay his hand surely on the mode of action of his particular hormone. (An exception may perhaps be made for the estrogen-activated transhydrogenase system.) But the other great problems of growth control in plants seem to be equally refractory: the biogenesis of indoleacetic acid, the peculiar interrelation between growth and oxidations, the role of metallic ions as cofactors in growth, the opposite responses of shoots and roots to applied auxins—all these problems and many more remain outside our understanding.

While many of these fundamental gaps in knowledge are brought out by Audus in this book, the impressive assemblage of factual material which he presents may tend to obscure them. One wonders whether the same vacuolated heart occurs in many other fields of physiology and biochemistry that seem, on the surface, to be making banner progress.

The new material makes this book some 90 pages longer than the first edition; the pages are somewhat larger, too. The chapter on the Chemistry of Auxins has been largely expanded and partly rewritten, and a noncommittal little section on anti-auxins has been added. A new chapter on the Mechanism of Action reviews the various approaches to this problem which have been made—the role of turgor in growth, evidence for action on the cell wall, action on the cytoplasm, and the interrelations with various aspects of metabolism. Other additions throughout the book deal in good part with the applications of growth substances in agriculture and horticulture. There is some treatment of the newer, non-auxin, phytotoxic agents, and a little here and there of the gibberellins. However, considering that the book is dated 1959, the amount of material published from 1955 onwards that has been included is somewhat disappointing.

In the chapter on Methods there are some small but important errors which would vitiate the results of anyone who might try to carry out the tests as described. The statement that it is equally satisfactory to melt agar with auxin or to soak 3% agar sheets in auxin solution ignores a clear demonstration to the contrary, in the literature for over 20 years. Plants used for the pea test are described as being grown in the dark, but later it is stated that their sensitivity can be increased by exposure to weak red light. The fact is that plants for this test are always grown with weak red light, and fully etiolated plants are almost unusable. The apical 5 mm are *not* removed, only the extreme "hook" is removed; the stem is slit to 2 cm, not 3 cm; the test is *not* very sensitive to traces of heavy metals, requiring 10^{-4} M $CuSO_4$ for inhibition—a concentration most unlikely to be present in distilled water; and the "greatest dilution which gives an observable response" could not be used as measure of auxin activity. *Avena* mesocotyls are not "much more sensitive to auxins" than coleoptiles, but only slightly so; the minimum amount of auxin determinable, 3–5 mμg, is about the same with this test as with the agar method on coleoptiles, which has the advantage of giving a linear rather than a logarithmic response. As a detail, it may as well be put on record that the ferric chloride and nitrous acid tests for indoleacetic acid are due to E. and H. Salkowski (1885), and not to the recent workers to whom Audus ascribes them. The photograph of curvatures in the *Avena* test is wretched and certainly gives no impression of quantitative reliability. On the other hand, there is a new diagram of four commonly used assay methods which presents a lot of material in clear summary form.

Throughout the book Audus offers a happy combination of fact with evaluation, and his critical judgment intervenes on many occasions to save the reader from drowning in a mass of contradictory or unconfirmable observations. This is true also in the extensive discussion of the practical applications of growth substances, in which he makes no attempt to oversimplify the situation, and balances the obvious advantages of treatment against the difficulties due to the varied sensitivities of different plants and the marked effects of age and conditions. This, the largest part of the book, is made readable for the "pure" scientist by the frequent interjection of theory, and of the principles of physiology and biochemistry. The chapter on auxins as initiators and stimulators of

fruit development is particularly thorough and reasonable. All in all, the feeling of balance, both of evidence and of topics, is perhaps the principal impression left with the reader.

The book is not expensive and should be widely useful.

KENNETH V. THIMANN

ECONOMIC BOTANY

BRITISH PLANT PATHOGENS. *A Host Parasite Index and a Guide to British Literature on the Fungus Diseases of Cultivated Plants.*

By W. C. Jones. Cambridge University Press, New York. $8.50. xvi + 430 pp. 1959.

The scope of this volume is well indicated by the title. In addition to fungi, a few actinomycetes and the diseases they cause are included, but none of the true bacteria, nor nematodes. A few myxomycetes, which, while not strictly plant pathogens in the usual sense, are capable of causing limited and local damage to cultivated plants, are also briefly listed.

There is a short introduction, followed by an alphabetical host index and an alphabetical list of the fungi known to cause damage to British plants. The hosts are listed by Latin names of genera or species or occasionally of family, with common names of hosts included and referred to the scientific name. Under each such name the parasites are listed, again with reference usually to a species, but sometimes to a genus. Occurrence in Britain and Ireland and pertinent references are given for each parasite, often with comments on control. Most references are brief, but in the case of important diseases several pages may be devoted to each. The scientific names are mostly those in common use; where names have been changed, this is noted, and commonly used synonyms are cited and cross-indexed.

While the book is intended for British workers, most of the diseases and the organisms associated with them are widely distributed, and the simple and eminently practical arrangement and concise summary of pertinent information, which make it convenient and easy to consult, will make this a valuable addition of the reference shelf of any laboratory where the organisms listed and the diseases they cause are studied.

G. W. MARTIN

MEDICINAL PLANTS OF THE ARID ZONES. *Arid Zone Research—XIII.*

UNESCO, Paris; Columbia University Press, New York. $3.00 (paper). 96 pp.; ill. 1960.

GENERAL AND SYSTEMATIC ZOOLOGY

DIE ENTDECKUNG NEUER ORGANISATIONSTYPEN IM TIERREICH.

By Peter Ax. A. Ziemsen Verlag, Wittenberg. 6.50 DM. 116 pp.; ill. 1960.

This seems to be a fashionable time for taking a second look at unprepossessing and ambiguous small creatures, and discovering to our surprise that the second glances involve major zoological reconsiderations. For years, perhaps, *Pogonophora* had been thrown back into the ocean as bits of frayed hawsers; *Neopilina* was unceremoniously tossed into formalin along with everything else from the sample; and numbers of small worms and arthropods had been politely ignored. Perhaps more zoologists should take a long look at some of the indecipherable material pushed to the back of the shelf years ago—who knows how many more surprises like *Hutchinsoniella, Zenoturbella, Neopilina,* and the like will turn up? This concise and well-illustrated account describes most of the recent discoveries and rediscoveries, including *Latimeria,* but not the bivalved gastropods. The morphology and significance of each organism is considered, and there is an excellent bibliography. This little book brings together a great deal of information previously available in the scattered specialist literature, and a translation would be most welcome.

JOEL W. HEDGPETH

A Translation of FAUNA OF U.S.S.R. ARACHNIDA, IXODID TICKS (IXODIDAE), *Vol. IV, No. 2.*

By P. I. Pomerantzev; translated by Alena Elbl; edited by George Anastos. American Institute of Biological Sciences, Washington. $10.00. 199 pp.; ill. 1959.

A Translation of FAUNA OF U.S.S.R. ARACHNOIDEA TYROGLYPHOIDEA (ACARI), *Vol. VI, No. 1.*

By A. A. Zakhvatkin; translated and edited by A. Ratcliffe and A. M. Hughes. American Institute of Biological Sciences, Washington. $10.00. vi + 573 pp.; ill. 1959.

During the past three decades, much important systematic work has been done in the U.S.S.R. in connection with the preparation of the *Fauna of U.S.S.R.* The volumes with which this reviewer is familiar are of high quality and are more in the nature of monographic revisions based on an extensive study of large collections than the more usual compilation-type of faunal account. The two volumes reviewed here are outstanding in that they not only give an account of the species found in various parts of the U.S.S.R. but also contribute a broader understanding of the groups in question.

Zakhvatkin's classification of the cheese and grain mites has been accepted as the first reasonable arrangement of these important animals. At least two other acarologists have subsequently arrived at his conclusions independently, since his work, first published in 1941, was not available to them. At the present time, this account of the Tyroglyphoidea is the most complete and most useful available. It is indispensable for the many acarologists and entomologists working on the numerous serious problems associated with grain storage, cheese production, and curing of meats. Not only is the work of Zakhvatkin outstanding, but the translation is smooth and clearly intelligible. Physically, the publication leaves much to be desired, but this is an economic problem, not an academic one. The book is done in photo-offset, or some similar method, so that the typography is that of a conventional typewriter. Lack of the versatility of printing, with its use of different type sizes and styles, makes it difficult to follow some of the keys, bibliographic references, diagnoses, etc. Fortunately, the photo-offset process has done justice to the line drawings that are so important in a taxonomic study of this kind.

Pomerantzev's account of the ticks of the U.S.S.R. is also outstanding, but its systematic value is limited to an understanding of the ticks of the U.S.S.R., since the basic classification of ticks has been well understood and accepted for the past fifty years. The volume is of particular interest to a wide audience, however, because of the many diseases transmitted to man and animals by ticks in Russia and also because of the detailed ecological observations accompanying the descriptions of the important and well-known species. The translation of Pomerantzev's volume was originally prepared in mimeographed form by the Institute of Acarology for the primary use of specialists in the systematics of ticks. The mimeographed translation was not modified in preparing this volume for a wide audience, and the translation is less polished, though not less accurate, than that of the volume on cheese mites. The typography, on the other hand, is better, since italics have been used.

Both of these volumes should be available to all biologists interested in entomology, acarology, parasitology, ecology, agriculture, and public health. The translators and the A.I.B.S. have rendered a great service to English-speaking zoologists by making these important Russian contributions available in English.

G. W. WHARTON

THE AFRICAN SPECIES OF THE GENUS *Cheumatopsyche* (TRICHOPTERA, HYDROPSYCHIDAE), AND THE EPHEMEROPTERA TYPES OF SPECIES. *Described by A. E. Eaton, R. McLachlan, and F. Walker. The British Museum (Natural History), London.* 20s. (paper). ii + pp. 256–318; ill. 1960.

A SYSTEMATIC MONOGRAPH OF THE DERMAPTERA OF THE WORLD *Based on Material in the British Museum (Natural History). Part 2: Pygidicranidae excluding Diplatyinae.*

By W. D. Hincks. The British Museum (Natural History), London. £3 10s. (paper). x + 218 pp.; ill. 1959.

The Dermaptera (earwigs) are a relatively minor order of orthopteroid insects, with a present total of about 1,200 known species. As is usually true for a neglected group, the present much-needed and thoroughly prepared *Monograph* brings together a scattered literature and is fundamental to future studies as well as indispensable for identifications. The author, of the Manchester Museum, England, has been the most active student of earwig systematics for some 20 years, in addition to carrying out avidly extensive work with Coleoptera and playing a leading role in broad studies of the British insect fauna.

The two parts of the *Monograph* which have appeared complete the coverage of the Pygidicranidae, a primitive family with 227 species. The great majority inhabit tropical countries. This work is based primarily on the collection of the British Museum, containing the material assembled by the late Malcolm Burr, whose studies were preeminent prior to 1920. In spite of the large number of specimens available, many species are far from adequately represented, so that, in view of the sketchy collecting which has been done in some rich areas of the tropics, the *Monograph* is more of a guide for future systematic work than it is a final "last word" for this order of interesting but neglected insects.

The *Monograph* is arranged for convenient use, with introductory portions containing helpful hints, and notes on classification and anatomy. The bibliography and index add to the completeness of documentation. Only a few minor errors have come to my attention. The author and sponsoring institution, The British Museum, are to be commended warmly for this excellent publication, and we may hope for the regular appearance of future parts of the *Monograph*.

ASHLEY B. GURNEY

LACE-BUG GENERA OF THE WORLD (HEMIPTERA: TINGIDAE). *Proc. U. S. Natl. Mus., Vol. 112, No. 3431.*

By Carl J. Drake and Florence A. Ruhoff. Smithsonian Institution, Washington. Free upon request (paper). 103 pp. + 9 pl.; text ill. 1960.

ASSASSIN BUGS OF THE GENUS *Ghilianella* IN THE AMERICAS (HEMIPTERA, REDUVIIDAE, EMESINAE). *Proc. U. S. Natl. Mus., Vol. 112, No. 3440.*

By J. Maldonado-Capriles. Smithsonian Institution, Washington. Free upon request (paper). Pp. 393–450; ill. 1960.

A Revision of the *Apion* Subgenus *Trichapion* Wagner in the New World (Coleoptera: Curculionidae). *Proc. U. S. Natl. Mus., Vol. 110, No. 3418.*

By David G. Kissinger. Smithsonian Institution, U. S. National Museum, Washington. Free upon request (paper). Pp. 247–389; ill. 1959.

The weevil genus *Apion* is a large, unwieldy genus, with 425 known species in the New World alone. It has been divided into a number of subgenera, of which 6 occur in the Americas. *Trichapion* Wagner is one of them, and 92 species of this subgenus are treated in the monograph. Most of the species are assigned for the first time to this subgenus by the author, among them several occurring in the United States; and 17 new species are described. As long as the whole of the genus in the New World is not known with similar thoroughness, it will not be easy for the non-specialist to find his way in the monograph, notwithstanding the keys and detailed descriptions given. The absence of an index does not make things easier. The author promises further contributions, so that eventually the entire genus should be known.

G. H. Dieke

Catalogue Commenté des Coléoptères du Maroc. *Fasc. VIII, Phytophages. Trav. Inst. Scient. Chérifien, Sér. Zool., No. 19.*

By Louis Kocher. Société des Sciences Naturelles et Physiques du Maroc, Rabat. 600 fr. (paper). 176 pp. 1958.

Contribution à L'Étude des Chrysomélides du Maroc. *Mem. Soc. Sci. nat. Maroc, Zool., No. 5.*

By Louis Kocher. Société des Sciences Naturelles et Physiques du Maroc, Paris and Rabat. 500 fr. (paper). 82 pp.; ill. 1958.

The first of these publications is a list of 519 species of the families *Cerambycidae, Chrysomelidae, Bruchidae,* and *Anthribidae* with localities in Morocco and critical remarks. Volumes 1–7 have appeared previously (since 1955).

The compilation of the *Catalog of Moroccan Beetles* (see preceding publication) has led the author to a critical study of some groups. The results of such a study on the Chrysomelidae are the subject of the second publication. It contains remarks on the taxonomic status of some known species or groups of species and the descriptions of 11 new species and a number of new subspecies and varieties. The treatment of the known species, based on the author's own observations, furnishes material that will be valuable later for a badly needed revision of parts of the family.

G. H. Dieke

North American Caterpillar Hunters of the Genera *Calosoma* and *Callisthenes* (Coleoptera, Carabidae). *Bull. Amer. Mus. Nat. Hist., Vol. 116, Art. 3.*

By Tatiana Gidaspow. The American Museum of Natural History, New York. $2.00 (paper). iv + pp. 229–343; ill. 1959.

This is the type of complete monograph that should be welcomed by anyone interested in such a group. It deals with the history of the taxonomy of the two genera and then gives detailed information on all the species known from North America, including Mexico. Three new species are described. The beetles of this group are, in general, fairly large. They are indigenous in all parts of the North American continent. At least one species (*Calosoma sycophanta* L.) has been introduced successfully from Europe for the control of the gypsy moth.

The author follows in general those European entomologists who have dealt in the recent past with the world-wide taxonomy of the genera, and follows a sensible middle path between the extremes of too much or too little subdivision of genera and species. There are keys and many figures which, better than a verbal description, make it possible to recognize the anatomical details on which the identification of the species depends.

G. H. Dieke

ANIMAL GROWTH AND DEVELOPMENT

A Guide to the Study of Development.

By William W. Newby. W. B. Saunders Company, Philadelphia and London. $4.00 (paper). xii + 217 pp.; ill. 1960.

The title of this book carefully avoids defining that the contents are those of a *laboratory* guide. An introductory note to the instructor makes clear, however, that its first aim is to aid the student in a conventional laboratory study of descriptive embryology through the examination of prepared microscope slides. Of the 18 chapters in the book, 8 are devoted to laboratory directions; these cover gametogenesis and a study of chick embryos (stages 1 through 20) and pig embryos (10 to 12 mm and 20 mm in length). The directions, which are extremely detailed, will be viewed favorably by instructors who wish to confine their laboratory exercises to the study of prepared slides of these particular stages of chick and pig.

The remaining 10 chapters, which are interspersed among the chapters containing the laboratory directions, discuss the life cycle of an animal, reproduction and fertilization, the physiology of development (4 chapters: the organization of the egg, the formation of the embyro, development of organs; and interrelationships of developing organs), mam-

malian development, abnormal development, and embryology and evolution. Actually, these chapters make up considerably more than ten-eighteenths of the book, since they are set in smaller type than most of the laboratory directions, and also, in contrast to most of the pages of laboratory directions, they are set in double rather than in single columns. They describe morphological material not covered in the laboratory directions, as well as many familiar experimental studies. They are illustrated by a considerable number of clear but simplified line and stippled drawings.

The legends to the illustrations refer only in a very few cases to the original sources. There are very few references in the text to journal articles, and the bibliography, numbering 14 entries in all, refers primarily to textbooks. One journal, *Developmental Biology*, is named, and incorrectly described as the only one devoted exclusively to development. The final chapter, on evolution and embryology, seems inappropriate, temperate though it may be in its views, for inclusion in what purports to be primarily a laboratory manual.

JANE OPPENHEIMER

THE AVIAN EMBRYO. *Structural and Functional Development.*

By Alexis L. Romanoff. The Macmillan Company, New York. $35.00. xviii + 1305 pp.; ill. 1960.

This book is a complementary and companion volume to *The Avian Egg*, which was published in 1949 (*Q.R.B.*, 24: 248. 1949). In attempting "to bring together in one volume all the known scientific facts about the structure and function of the avian embryo," the author has set for himself a Herculean task, a task that is, in fact, impossible of accomplishment. He has, however, succeeded in bringing together a large amount of factual information which is extremely useful not only to workers interested in the chick embryo but also to those interested in the embryos of other birds. Since much of the work done on bird embryos, other than those of the ordinary domestic fowl, is scattered widely in ornithological and other publications, often quite inaccessible, the author has, in his searching survey, rendered a real service.

The statements in the book are documented with a bibliography of nearly 3000 titles, over half of which are in foreign languages. It is helpful indeed to find all of these in one place, at the end of the text, arranged alphabetically according to the authors' names, and with page references. There is also a very good subject index. Such features contribute greatly to the usefulness of the vast amount of material included in the volume.

In organization and style the book is typically a "textbook." There are 13 chapters with the following headings: The Reproductive Cells; Fertilization and Fertility; Early Morphogenesis; The Nervous System; The Organs of Special Sense; The Digestive System; The Respiratory System; The Hematopoietic, Vascular and Lymphatic Systems; The Heart; The Urogenital System; The Endocrine Glands; The Skeletal System and the Integument; The Extraembryonic Membranes. When one considers the attention given to the various organ systems, it is rather surprising to find so little information on The Muscular System. The origin and development of the muscles of the trunk and limbs are, except for a few passing references, virtually ignored.

In any all-embracing effort of this kind defects and errors are inevitable, and this book is no exception. The author, without being truly critical, has been primarily concerned with recording what investigators have reported in the literature. There is no indication as to which experiments are "good" and which are not; but perhaps this would be too much to expect in such a wide-ranging compendium compiled by a single author. Hence investigators interested in a particular area will find it necessary to consult the original publications referred to. Of importance, however, is the fact that from this book one can get a very good idea of what has already been done in a particular field.

In an over-all evaluation of the book it must be emphasized that it is not a critique but a source of factual information. As a source book it has much to commend it to all biologists—students, teachers, investigators—who are interested in this most remarkable and important class of vertebrates.

MARY E. RAWLES

DEVELOPMENTAL BIOLOGY. *Vol. 1, No. 1.*

Editorial Board: Jean Brachet, Ernst Hadorn, and Paul Weiss; managing editor: M. V. Edds, Jr. Academic Press, New York and London. $14.00 (6 issues; paper). x + 126 pp.; ill. 1959.

It is the custom of this *Quarterly* to notice the appearance of new periodicals of importance by reviewing the first number of each to appear. It would seem a trifle fruitless in November 1960, when this comment is being written, to itemize the contents of a number that has already been followed by 10 others. Instead, we might place the new journal in sequence with some of its peers devoted to developmental problems. It joins, among others, the *Zeitschrift für Anatomie und Entwicklungsgeschichte* (Munich, 1891), *Roux' Archiv für Entwicklungsmechanik der Organismen* (Leipzig, 1894), *Arkhiv Anatomii, Gistologii i Embriologii* (Leningrad, 1916), *Embryologia* (Nagoya, 1950), the *Journal of Embryology and Experimental Morphology* (Oxford, 1953), and

Acta Embryologiae et Morphologiae Experimentalis (Palermo, 1957). Thus many developmental biologists have made journals; how many journals have made developmental biologists? Without any false illusions about the significance of new journals, as such, as being determining factors for embryological progress (*Roux' Archiv* was the exception, not the rule), we wish the new periodical success for whatever it may add to, rather than subtract from, our knowledge and understanding of development.

JANE OPPENHEIMER

ANIMAL MORPHOLOGY

THE HUMAN INTEGUMENT. *Normal and Abnormal. A symposium presented on Dec. 28–29, 1957, at the Indianapolis meeting of the AAAS and cosponsored by the Committee on Cosmetics of the American Medical Association and the Society for Investigative Dermatology. Publ. No. 54.*

Edited by Stephen Rothman. American Association for the Advancement of Science. Washington. $5.75; $5.00 (AAAS Members). x + 260 pp. + 3 pl.; text ill. 1959.

This small volume contains 12 papers which fall into four groups: The integument as an organ of protection; Circulation and vascular reaction; Sebaceous gland secretion; and Pathogenetic factors in premalignant conditions and malignancies of the skin. In the selection of topics the editor states that an attempt was made to choose those that illustrate what is being achieved in cutaneous physiology and pathophysiology, by means of modern methods, with the hope of course of stimulating future dermatological research.

As a whole, the papers are presented in a simple form easily understandable to readers who do not necessarily have that background knowledge of recent biological research often assumed in articles written by specialists for their own colleagues. Although the emphasis throughout is on clinical applications, there are in various reports examples which illustrate the advancements that have been made through a successful correlation of structure and function. Such symposia are of value in that they give physicians in clinical practice an account of fundamental research in areas of particular interest to them.

MARY E. RAWLES

LYMPHOCYTES AND MAST CELLS.

By Margaret A. Kelsall and Edward D. Crabb. The Williams & Wilkins Company, Baltimore. $8.00. xvi + 399 pp.; ill. 1959.

The contents of this book range from discussions of lymphocytes, plasma cells, and mast cells, to gammaglobulins, hyaluronic acid, heparin, histamine, and serotonin, and thence to the thymus, spleen, and bone marrow, followed by inflammation and wound healing. There is a detailed discussion of the distribution of mast cells, of factors modifying the number of mast cells, of vasomotion and capillary permeability, of the vascularity of the spleen, of intestinal lymphoid tissue, and of the fibroblast. Coprophagy and carcinogenesis are also discussed. The approach to the various subjects is literary rather than factual. Conclusions are drawn from references, rather than from experimental or statistical observations. The references, however, are well chosen, and 1142 books and papers are cited. That lymphocytes, plasma cells, and mast cells are trephocytes is not proven by this book, but the authors have brought together all the evidence which they feel supports their thesis. Many statements are difficult to defend. There is no reason to believe, for instance, that "primarily, the formation of plasmacytes is a process of withdrawing protein from extracellular fluid and storing it intracellularly to aid in the regulation of protein synthesis in other cells," or that the absence of plasma cells in the thymus is explained by absence of lymph stasis which "may furnish an important stimulus for transformation of plasmacytes from lymphocytes in lymph nodes and spleen." Whatever shortcomings this book may have, however, the authors have performed a good service by reminding us that the view that the lymphocyte is merely an undifferentiated mesenchymal cell capable of developing into other cells is by no means established.

WILLIAM E. EHRICH

ANIMAL PHYSIOLOGY

PROGRESS IN THE BIOLOGICAL SCIENCES IN RELATION TO DERMATOLOGY. *Thirty-seven papers delivered in Cambridge at a course for physicians in clinical practice.*

Edited by Arthur Rook. Cambridge University Press, New York and London. $15.00 xvi + 480 pp. + 24 pl.; text ill. 1960.

The 37 papers which make up this informative and useful volume record a course of lectures, given by invitation, in the Postgraduate Medical School of the University of Cambridge during September, 1958. The main purpose of this course, the first of a contemplated series, was to give physicians in clinical practice an up-to-date account of the findings that have come from modern experimental approaches to important dermatological problems; in other words, to intergate medical science with clinical practice. Dermatology seems a wise choice for the start of a program of this kind, for during the past two

decades it has truly undergone a renaissance. At the present time it is realized rather generally that the skin is one of the most complex organs of the body and a sensitive indicator of the condition of the great variety of tissues it invests.

The papers were presented in eleven sessions and are grouped under the following general headings: The melanocyte and melanogenesis; Cutaneous innervation; Histochemical investigations; Bacteriology and mycology; Psychophysiological mechanisms; Comparative medicine; Immunology; Inflammation; Carcinogenesis; Radiation and the skin; Pharmacology. Edited and abridged reports of the discussions that followed each session add much interest in showing the exchange of views between basic scientists and clinicians.

One of the chief values of a book of this type is that it gathers together material widely scattered in many journals, some quite inaccessible, and presents it in a form readily understandable to clinicians and others who may not have sufficient background knowledge or training in modern research methods to comprehend fully the details of the articles as originally written.

The volume is well edited and well indexed. Many of the papers are illustrated.

MARY E. RAWLES

FOURTH TISSUE HOMOTRANSPLANTATION CONFERENCE. *Ann. N. Y. Acad. Sci., Vol. 87, Art. 1.*

John M. Converse and Blair O. Rogers (Conference Co-Chairman) with 101 contributors. The New York Academy of Sciences, New York. $5.00 (paper). 607 pp.; ill. 1960.

The proceedings of the fourth biennial conference on tissue homotransplantation are divided into five sections, on the topics: histocompatibility; experimentally induced modifications of responses to tissue transplants; antigen-antibody manifestations; immunological tolerance; and organ transplantation. A considerable body of the material is devoted to an elucidation of the number of "histocompatibility genes" in various materials, biological assays for effects such as gene dosage and various strengths of the various genes (or, more properly, the gene-products responsible for the effects), etc. Details of the tissue rejection patterns themselves have received considerable attention, and much effort has gone into determining how general, phylogenetically, such reaction patterns are. There is still a striking absence of attempts to characterize the chemical nature of the effective antigens involved in single systems, and there is comparatively little effort to search for the basic immunological mechanisms of great rejection by tests of classical immunology. Welcome new trends concern passive transfer experiments and studies on the actions, in vitro, of various sera on particular cell types. Furthermore, one notes that homotransplantation research is evolving from a discipline with special interests to a much less restricted area of investigation, sharing many problems in common with other branches of immunology.

PHILIP E. HARTMAN

METABOLISM IN THE RUMEN. *Methuen Monograph. By E. F. Annison and Dyfed Lewis. John Wiley & Sons, New York.* $2.75. 184 pp. 1959.

The authors describe this monograph as an attempt "to survey the available knowledge on metabolic activities in the rumen," but the monograph accomplishes a great deal more than this. For one who has been concerned primarily with the physiology and metabolism of monogastric animals, this monograph is bound to be very stimulating and informative. In a consise, yet readable, presentation one is exposed to a critical, well-documented summary of the current knowledge concerning the interactions between ingested materials and the rumen microflora. Many nutritional and metabolic advantages and problems peculiar to ruminant animals are pointed out. Of great value to the reader is the devotion of considerable space to a discussion of experimental techniques which have been employed in the study of rumen metabolism, and to the limitations of the techniques currently available.

The monograph begins with a brief introductory chapter to orient the reader with respect to the anatomy and physiology of the rumen, and to point out some of the contrasts betweeen the nutrition of polygastric and monogastric animals. The second chapter discusses the nature of the mircobiological population of the rumen and the general types of chemical conversions attributed to various classes of microorganisms. A chapter entitled Carbohydrates and Fatty Acids is chiefly concerned with the production of the volatile fatty acids from cellulose, starch, other plant polysaccharides, and the simple sugars. The chapter on Nitrogen Metabolism discusses such phenomena as protein hydrolysis, amino acid degradation and synthesis, and the significance of bacterial protein to the nutrition of ruminants. Absorption from the rumen is discussed in some detail.

The final chapter is perhaps the most intriguing. Entitled Rumen Function and Dysfunction, it considers in some detail the relations between the metabolism of the ruminant and metabolism in the rumen. The authors point out the influence of the rumen organisms on the energy metabolism of the host animal, and the profound effect of these organisms on the apparent nutritional requirements of the host with respect to fats, vitamins, and minerals. The significance of various disturbances of rumen function are also discussed.

This monograph should be of interest and benefit to biologists of many different orientations.

K. J. MONTY

SELECTIVE TOXICITY.

By Adrien Albert. John Wiley & Sons, New York; Methuen & Co., London. $5.50. x + 233 pp. + 5 pl.; text ill. 1960.

It is impossible for the experienced researcher or neophyte to open this text at random and read, without being seductively led on and on into entertaining byways of provocative investigational "leads." The concept of selective toxicity refers to those chemicals which injure some kinds of cells but not others, even when the two are growing close together. Indeed, this is the basis of therapeutic drug action, and the subject leads naturally into a discussion of the mode of action of drugs and other biologically potent substances.

The second edition includes new features: absorption and distribution as related to avenue of administration and degradation; pharmacodynamics, which resembles a pharmacology textbook description; covalency, including the newer concepts of penicillin binding; surface chemistry, and the modification of membranes by drugs; and steric factors, stressing what seems important about the size and shape of biologically active molecules. Modern concepts have been introduced in other chapters. For example, the discussion of ionization and the relations of pK_a values to pharmacologic effects is one of the best this reviewer has encountered. Examples are cited and a table is given in the appendix for calculating the percentage ionized for a stated compound if the pK_a and pH are known or vice versa. This table is a useful tool that is not readily found outside of physical chemistry tomes.

Undergraduate students and advanced research workers in the biological sciences will find many helpful ideas in the book.

C. JELLEFF CARR

COMPARATIVE CLINICAL AND BIOLOGICAL EFFECTS OF ALKYLATING AGENTS. *Ann. N. Y. Acad. Sci., Vol. 68, Art. 3.*

By Leon H. Schmidt and 108 other contributors. The New York Academy of Sciences. New York. (paper). Pp. 657–1266; ill. 1958.

Reviews of the rather scanty knowledge concerning the chemistry of alkylating agents and their reactions with biologically important molecules serve as the introductory portion of this monograph. Some of the "chemistry" described actually deals more in the realm of biological effects, which are further covered in Part two. The gross biological observations seem so far to contribute little to our understanding of the mode of action, in vivo, of alkylating agents and to reflect the paucity of information available at the biochemical level. Approximately three-fourths of the contents of this volume constitute descriptions of clinical results with a variety of alkylating agents and demonstrate the value of these drugs in human cancer therapy. With an increasingly wide spectrum of variously substituted molecules becoming available for clinical trial, clinical studies are now largely concerned with screening new compounds and comparing their effects with more widely used standards rather than investigating the mode of action of such drugs. Articles by A. Gelhorn and C. G. Zubrod, respectively, succinctly summarize necessary criteria for these comparative evaluations and procedures for clinical trials. The last portion of the symposium, noted as "summary and discussion," except for a very general and short paper by Gelhorn, neither summarizes nor discusses the results reported in the preceding massive contents.

PHILIP E. HARTMAN

NONNARCOTIC DRUGS FOR THE RELIEF OF PAIN AND THEIR MECHANISM OF ACTION. *Ann. N. Y. Acad. Sci., Vol. 86, Art. 1.*

By Frank M. Berger and 50 other contributors. The New York Academy of Sciences, New York. $3.50 (paper). 310 pp.; ill. 1960.

A large number of specialists have reviewed the physiology and pharmacology of pain in this monograph, which also includes reviews of some new analgesic agents. Experimental methods used in animal studies and in man are described. The drugs considered include the salicylates and related compounds, carisoprodol, zoxazolamine, chlorzoxazone, phenyramidol, and phenylbutazone and its analogues. It is of interest that most workers do not feel that research in this area has kept pace with the rapid improvements in other drug therapies.

C. JELLEFF CARR

INTERNATIONAL REVIEW OF NEUROBIOLOGY. *Volume 2.*

Edited by Carl C. Pfeiffer and John Smythies. Academic Press, New York and London. $11.00. xii + 410 pp.; ill. 1960.

The following subjects are reviewed in this volume: Regeneration of the optic nerves in amphibia (R. Gaze); Experimentally induced changes in the free selection of ethanol (J. Mardones); The mechanism of action of the hemicholiniums (F. Schueler); The role of phosphatidic acid and phosphoinositide in transmembrane transport elicited by acetylcholine and other humoral agents (L. E. Hokin and M. R. Hokin); Brain neurohormones and critical epinephrine pressor responses as affected by schizophrenic

serum (E. Walaszek); The role of serotonin in neurobiology (E. Costa); Drugs and the conditioned coordinance response (A. Herz); Metabolic and neurophysiological roles of gamma-aminobutyric acid (E. Roberts and E. Eidelberg); and Objective psychological tests and the assessment of drug effects (H. Eysenck).

All of the reviews appear to be well written and critical towards their subject matter. They also all appear to be quite up to date. The paper by Mardones was most interesting. He points out that a comparison of human alcoholism with experiments involving animal consumption of alcohol is quite difficult. Animals do not appear to become addicted to alcohol in that they show no withdrawal symptoms. However, many factors affect animal consumption of alcohol, and it can be assumed that some of these same factors will also affect humans.

The article by Costa on serotonin gives a good picture of current research on this neurohormone. Some workers implicate serotonin in the majority of mental disorders. Yet others feel that the metabolism of serotonin is entirely unrelated to the physiological events occurring in the brain. Costa feels that the truth falls somewhere between these views, and he marshals the evidence in clear-cut fashion so as to support his opinion. All in all, the book maintains the high standards set by the first volume of this series.

M. L. WOLBARSHT

SECOND CONFERENCE ON PHYSICOCHEMICAL MECHANISM OF NERVE ACTIVITY AND SECOND CONFERENCE ON MUSCULAR CONTRACTION. *Ann. N. Y. Acad. Sci., Vol. 81, Art. 2.*

By David A. Nachmansohn and Alexander Sandow and 27 other contributors. The New York Academy of Sciences, New York. $4.00 (paper). iv + pp. 219–509; ill. 1959.

This monograph contains the papers presented at two conferences held in October, 1958. The section on nerve covers the physical and chemical aspects of nerve conduction, neuromuscular and synaptic transmission, and sensory receptors. The contributors are Andrew Huxley, J. C. Eccles, R. Stampfli, E. Schoffeniels, I. B. Wilson, W. Nastuk, W. Riker, Jr., C. Chagas, Y. Zotterman, W. Lowenstein, Ruth Hubbard, and Allan Kropf. The various papers presented include both reviews and presentations of new material. The twelve years between the first New York Academy conference on nerve activity and those reported here saw the most significant advances in the field since the discovery of the action potential. The Hodgkin-Huxley equations were enunciated and confirmed, chemical transmission at the synapse was established, and the excitatory and inhibitory postsynaptic potentials were discovered. All of these subjects are covered thoroughly here, and enough new material is included to make this a useful reference for the expert in the field.

The section on muscular contraction includes papers by Jean Hanson, Hugh Huxley, Andrew Huxley, H. H. Weber, T. Buchthal, O. Sten-Kundsen, A. Csapo, R. Davies, B. Chance, J. Gergely and F. Jobsis. Again the papers are of both types, those which present new data and those which review the field. While there have been several significant advances in the study of muscular contraction since 1946, notably the interdigitating filament model, local activation, and relaxing factor, no clear picture of the mechanochemistry of muscle has emerged that corresponds to that given by the Hodgkin-Huxley Theory of ion movements in nerve. It is of interest to note in this connection that, in the case of nerve, experimentation has for the most part been confined to intact neurons, whereas in the case of muscle, extracts and models have been the major materials used for mechanochemical investigations, and only recently have chemical studies on the intact cell been reported.

F. D. CARLSON

BIOPHYSICS AND GENERAL PHYSIOLOGY

BIOLOGICAL ORGANISATION, *Cellular and Sub-Cellular. Proceedings of a Symposium organised on behalf of UNESCO and held at the University of Edinburgh, Scotland, September, 1957.*

Edited by C. H. Waddington. Pergamon Press, New York, London, Paris, and Los Angeles. $12.00. xviii + 328 pp.; ill. 1959.

The subject of this book is an obviously important and pertinent one, for it encompasses most of the profound questions being raised in biology today. The presentation of the proceedings as an edited tape recording (and not very well edited at that) is something else again, and the prefatory statement of the editor that such a presentation permits the graduate student profitably to sit in, as it were, on the intellectual word play of his peers is so much patronizing nonsense. All too frequently the pursuit of a particular subject is segmented by questions and discussions which divert or dilute, is obscured by a discussion which relates to a lantern slide or blackboard diagram which is missing, or is abandoned because a more forceful virtuoso seized an opportunity to play his own fiddle. Only the sophisticated will be able to follow this with profit. And few of the major discussants—Paul Weiss and S. Brenner are exceptions—speak as well as they write.

The scope of the symposium deals with organiza-

tion from the levels attainable with the electron microscope to tissues in a somewhat more macroscopic sense, with the biochemistry of organization supposedly, but not too successfully, avoided. The purpose of the symposium was, to use Waddington's terms, "to discuss the bearing of the results we have obtained, the nature of the problems we are trying to solve, and how they are related to one another." This was done by considering first the nature of organization in biological terms, a knotty problem at best and handled in typical Weissian fashion, and then proceeding from the genetic level to succeeding ones of higher complexity. Since most of the material discussed has by now been published elsewhere, there is no need for a comprehensive review of the major topics. However, the contents of the volume can very well be judged by a listing of the major subdivisions of the program and principal discussants: Nature of biological organization (C. H. Waddington and P. Weiss); Organization at the level of the gene (S. Brenner and G. Pontecorvo); Organization of the chromosome (H. Callan, J. Gall, H. Ris, W. Plaut, W. Beermann, and C. Pavan); Functional nucleo-cytoplasmic interactions (Waddington, Plaut, and Weiss); Morphological organization of nucleus and cytoplasm (Helen Gay); Activities of the cytoplasm (G. H. Beale, H. Holtzer, F. E. Lehmann, and J. Gustafson); Chemical organization of the cell (Waddington, A. C. R. Dean, and M. R. Pollock); Tissue interactions (C. E. Wilde, S. Toivonen, P. D. Nieuwkoop, and J. Brachet); Organization of tissues into organs (E. Zwilling, Waddington, and Nieuwkoop); Organization of growth processes (H. P. Rusch and I. Berenblum); and cell division (M. Mitchison, Lehmann, and K. Dan).

C. P. Swanson

Advances in Biological and Medical Physics. *Volume VII.*

Edited by Cornelius A. Tobias and John H. Lawrence. Academic Press, New York and London. $10.00. x + 362 pp.; ill. 1960.

Three of the articles contained in this volume are concerned with the effects of high energy radiation on biological material: Genetic and physiological effects of the decay of incorporated radioactive phosphorus in bacterial viruses and bacteria (G. Stent and C. Fuerst); Radiation carcinogenesis (L. Law); and Physiological effects of nuclear radiations on the central nervous system (N. N. Livshits). The last article is especially valuable because the author, who is a member of the Academy of Sciences of the U.S.S.R., has considered critically a large body of Russian literature on the subject which is not readily available in English. This remark does not suggest that he has slighted the non-Russian literature, for that is also rather completely covered. In addition to the usual list of references, this article also has a supplementary list covering publications in 1959 and 1960. However, none of these are mentioned in the text and one can only speculate as to the reason for their inclusion.

Several of the articles are concerned mainly with techniques: Micro-X-ray diffraction on biological materials (D. Carlström); Audoradiography with tritrium-labeled substances (J. H. Taylor); and Some isotopic studies on the distribution and metabolism of plasma proteins (D. Gitlin and C. Janeway).

The article by Lipetz, The *Limulus* eye as an Information Converter: Mechanisms for the Transfer of Information of the Light Image to the Optic Nerve Discharge, contains much previously unpublished work by the author. It brings into critical focus one of the major problems of visual research today, the correlation between structure and function in the retina. The *Limulus* lateral eye is admirably suited for this type of analysis. Work in this field will certainly furnish ideas for experiments in more complex vertebrate material.

M. L. Wolbarsht

Biological and Medical Electronics.

By Ralph W. Stacy. McGraw-Hill Book Company, New York, Toronto, and London. $9.50. xii + 308 pp.; ill. 1960.

This book is based on the textbook for a 10-week course by the Biophysics Division of the Physiology Department, Ohio State University, which consisted of one lecture hour and six laboratory hours per week. The 11 sections cover the fundamentals of electricity, vacuum tubes, and electronic circuitry. Detecting and sensing elements are covered thoroughly as are recording and readout devices. The section on complete instrumentation setups is particularly well done. Good examples are given of setups for displaying bioelectric potentials such as nerve, action potentials, and cardiovascular potentials. Trouble-shooting hints and the problems of interference are mentioned but not in quite as much detail as would seem necessary for the novice. Two additional sections on transistors and computers are both very good. The one on transistors contains many practical hints. The one on computers is short but to the point.

The book is designed as an elementary textbook; no calculus is used. It is at the level of medical students and biologists (one almost might say at the high school level). There are so many illustrations of components that one wonders whether they are really worthwhile. They increase the price of the book and fill up valuable space more than is warranted. A view of the outside of a piece of

equipment really tells you practically nothing about its value or usefulness.

Several points of the book may be mentioned. Strain gauges are covered in great detail. There is a good analysis of oscilloscopes. Some drawbacks are that there is no mention of grid current; input impedance is almost neglected; and the problem of electrometer tube microphonics is also omitted. Several of the circuits are not labeled properly, or do not illustrate the point under discussion. There is no sense in using P-N-P and N-P-N transistors in a circuit unless it is a DC circuit, which it is not in the illustration given. Under recording methods there is no mention of the use of paper instead of film. However, as a very elementary textbook the work would be hard to improve upon very much; for more advanced students it is too elementary. One hopes that the workers in this field will have more training than this book provides, but all medical students and biologists who are not specialists in medical electronics can read the volume with profit. It won't make them into electrophysiologists, but it will enable them to understand some of the problems facing electrophysiologists.

M. L. WOLBARSHT

FAST FUNDAMENTAL TRANSFER PROCESS IN AQUEOUS BIOMOLECULAR SYSTEMS.

Foreward by Francis O. Schmitt. Dept. of Biology, Massachusetts Institute of Technology, Cambridge. (paper). vi + 56 pp. 1960.

BIOCHEMISTRY

ULTRAFILTRATION. *A Monograph in Biochemistry and Biophysics. American Lecture Series. Publ. No. 408.*

By L. Ambard and S. Trautmann; preface by A. A. Monnier. Charles C Thomas, Springfield, Ill. $4.50. x + 67 pp.; ill. 1960.

ANNUAL REVIEW OF BIOCHEMISTRY. *Volume 29.*

Edited by J. Murray Luck; associate editors, Frank W. Allen and Gordon Mackinney. Annual Reviews, Palo Alto. $7.00. viii +786 pp.; ill. 1960.

Once again the editors have produced an exceptional collection of review articles dealing with recent achievements in biochemistry and allied fields. In addition to excellent reviews concerning various aspects of carbohydrates, amino acids, proteins, lipids, etc., there are reviews on sulfur compounds, neurochemistry, vitamins, nucleic acids, viruses, genetic factors, protein hormones, cancer, immunochemistry, clinical chemistry, gas chromatography, biological oxidations, enzymes, and a new grouping of enzymes under the heading of "transferases." In addition, the prefatory chapter by the late H. O. L. Fischer, son of the great Emil Fischer, is a fascinating reminiscence by a distinguished chemist. The usual high quality of writing found in previous volumes prevails; indeed, the reviews seem more lucid in this volume than in previous ones. Perhaps one's ability to digest this already digested form of writing increases with practice. Of exceptional quality were the reviews of protein biosynthesis and genetic factors.

A number of new departures in format have been taken in this volume. The bibliography at the end of each review is set in two columns and is much easier to read. There is also a cumulative index for chapter titles and for contributing authors for the past nine volumes. Both of these features are welcome and should be noted by editors of similar works. This volume also contains an author index listing every author cited in the text, and a very detailed and useful subject index.

EDWARD GLASSMAN

THE HUMAN BLOOD PROTEINS. *Methods of Examination and their Clinical Practical Significance. Translation from the Third Edition.*

By Ferdinand Wuhrmann and Charlie Wunderly. Grune & Stratton, New York and London. $15.75. xii + 491 pp.; ill. 1960.

This volume inaugurates the English translation of a well-known monograph which is directed toward the clinician interested in the diagnosis of numerous pathological conditions through an examination of the blood proteins. Although chemical tests are discussed, much of this book is devoted to alterations in the physical properties of the proteins under disease conditions. Zone and boundary electrophoresis studies occupy a particularly prominent position. The authors bring together in 7 chapters a truly impressive accumulation of information which should be of great value to the clinician as well as the clinically oriented protein chemist. The first three chapters, entitled Chemistry of the Plasma Proteins, Reactions of Proteins, and Methods of Examination, discuss the general properties of the blood proteins and the analytical methods which are used in characterizing them. Chapter 4, Clinical Chemical Methods, briefly describes such chemical procedures used in the clinical laboratory to evaluate changes in the blood system as the erythrocyte sedimentation techniques and the various turbidity and flocculation reactions. The Clinical Significance of the Plasma Proteins and Clinical Significance of Dysproteinemia and Paraproteinemia are considered in Chapters 5 and 6. Chapter 7 concludes the volume with a short ac-

count of The Formation and Synthesis of the Blood Proteins.

Unfortunately, the high level maintained in covering the literature is not always balanced by an equally critical approach in evaluating the physical data. Many protein chemists will feel somewhat uneasy about accepting conclusions based on incomplete electrophoretic or ultracentrifuge studies, particularly when these are used as the basis of diagnosis. The translation is generally good but is marred in the first three chapters by an unusually large number of errors.

WILLIAM HARRINGTON

NUCLEOPROTEINS. *Proceedings of the 11th Solvay Conference on Chemistry, Brussels, June 1–6, 1959. R. Stoops, Bruxelles; Interscience Publishers, New York.* $10.50. 364 pp.; ill. 1960.

Research workers and students closely following developments in nucleic acid chemistry and the biological functions of nucleic acids will be interested in this publication. Extensive discussions, constituting a valuable portion of the publication, follow each of the ten articles. The discussions often lead to clear delineations of some of the important problems for which answers are still to be sought. However, the comments also often tend to "date" the meeting and bring to one's attention the rapid advances constantly being made in this area of research. Nucleoproteins, per se, are considered extensively only in a résumé by M. H. F. Wilkins of interpretations of X-ray diffraction studies of nucleoprotein fibers. With the further exception of a paper on histones, by S. Moore, the articles are concerned almost exclusively with recent researches on natural and synthetic polynucleotides: their structure, interactions, distribution in nature, and their reactions to chemical and physical agents in vitro.

PHILIP E. HARTMAN

POLYSACCHARIDES OF MICRO-ORGANISMS. *By M. Stacey and S. A. Barker. Oxford University Press, New York and London.* 30s x + 228 pp. + 8 pl. 1960.

In this volume, the chemical literature on microbial polysaccharides has been brought together in a form which is useful as a reference work for carbohydrate chemists, as a clear introduction to the subject for microbiologists and "all those interested in the biology of macromolecules." The introductory chapters, constituting about a third of the book, describe some fundamentals of carbohydrate nomenclature, basic features of polysaccharide structure, and procedures for the isolation and characterization (including "fine structure" chemistry) of these macromolecules. Each of the remaining chapters surveys the present state of knowledge about the polysaccharides contained in some particular group of microorganisms (e.g., Gram-positive bacteria, molds, or protozoa). While immunological studies are mentioned in the surveys, the contributions of immunologists, particularly the Japanese workers, have been omitted in many instances. Abbreviated references, through 1959, follow each chapter, and an adequate subject index is provided the research worker.

The authors show quite well that "... we are at the beginning of a new era in microbial polysaccharide chemistry ...," but they do not go beyond this. The introductory chapter on the functions of polysaccharides does little to give a non-specialist any idea of the importance of polysaccharides to the organism. Very close examination of the detailed information summarized here is required if the reader is to gain some realization of the applications of this information, which, in conjunction with immunological and pharmacological studies, will in time allow resolution of many important biological and medical problems.

PHILIP E. HARTMAN

BIOCHEMISTRY OF STEROIDS. *Organic Chemistry and Biochemistry Textbook Series. By Erich Heftman and Erich Mosettig. Reinhold Publishing Company, New York; Chapman & Hall, London.* $6.90. xiv + 231 pp.; ill. 1960.

The term "biochemistry of steroids" is still restricted today largely to information respecting the biosynthesis and metabolic catabolism of these compounds. This book is a comprehensive survey of that knowledge and is properly set between the chemistry and pharmacologic actions of these complex molecules. The book also describes generally the techniques used in analysis, but the lack of specific references limits the usefulness of these sections. A general bibliography of over 700 references is provided and is classified according to the pattern of the book's text.

This book is best suited to provide an introduction to the field of steroids. It should appeal to many of the research workers in the basic and clinical sciences of medicine who approach this field with trepidation and timidity because of its complexity.

EDWARD B. TRUITT

ADVANCES IN CLINICAL CHEMISTRY. *Volume 3. Edited by Harry Sobotka and C. P. Stewart. Academic Press, New York and London.* $12.00. xiv + 400 pp.; ill. 1960.

The third volume of this series resembles the two

earlier ones in ranging over wide fields of interests essential to the clinical chemist in his work of applying the concepts and methods of chemistry to medicine. It offers 6 reviews of topics which are currently playing an essential part in the progress of medical science.

Infrared Absorption Analysis of Tissue Constituents, Particularly Tissue Lipids by Henry P. Schwarz, describes briefly the technique of infrared spectrophotometry in general with special application to phospholipids, sphingolipids, and fatty acids. Lesser mention is made of the examination of carbohydrates and nucleic acids of various tissues.

The article on The Chemical Basis of Kernicterus by Irwin M. Arias, is a complement to the chapter on bile pigments which is in Vol. 2. In 1956 it was demonstrated that bilirubin is conjugated primarily with glucuronic acid prior to its excretion in the bile. The review reports advances made since 1956 toward elucidating the cause of kernicterus and the methods used in the study of bilirubin conjugation. The conclusion to be drawn at present is that some factor (or factors) other than hyperbilirubinemia per se is responsible for damage of the central nervous system in kernicterus.

'Flocculation Tests and Their Application to the Study of Liver Disease,' by John C. Reinhold, is an excellent summary of the applications of the countless flocculation tests used for the study of changes in composition of the serum proteins and lipids that are prevalent in liver disease. The measurement of zinc turbidity, the cephalin-cholesterol flocculation test, and the thymol test receive especially detailed consideration. It is important to note that the continued use of flocculation tests seems entirely justified despite the fact that zone electrophoresis, which is capable of providing more specific evidence of changes in serum protein components, has become generally available. Various workers have concluded that most of the information yielded by electrophoretic studies was not essential in diagnosis; that which was essential could be obtained more readily by other less complicated methods, among them the flocculation tests.

The chapter on the natural estrogens, by J. B. Brown, deals not only with methods of determining 17 β-estradiol, estrone, and estriol in urine and blood, but also with their chemistry and their metabolism. The assay methods for measuring estrogens are beset with many shortcomings and are too elaborate to be employed occasionally in a routine clinical laboratory. Estrogens form an orange-yellow color with an intense greenish fluorescence when heated with concentrated sulfuric acid. This "Kober" reaction is the basis of fluorimetric and colorimetric methods. Recently Ittrich has introduced a procedure for purifying the Kober color whereby one can estimate estrogens in pregnancy urine by performing the reaction directly on the urine, and in menstrual cycle urine after a cursory purification procedure. The Ittrich method may well prove to be a significant advancement in estrogen methodology (*Clin. Chim. Acta*, 5: 544–551. 1960).

Folic Acid, Its Analogs and Antagonists, a review by Ronald H. Girdwood, covers the knowledge of the metabolic functions of folic acid, the actions of the folic acid antagonists, and the various clinical states in which folic acid deficiency is found. Microbiological assay methods for measuring folic acid are presented along with possible methods of measuring folic acid deficiency in the body. Much remains to be explained, particularly as regards the interrelationships of folic acid and vitamin B_{12}.

In the last chapter, by Ralph Gräsbeck, on the 'Physiology and Pathology of Vitamin B_{12} Absorption, Distribution and Excretion', the general viewpoint is physiological and nutritional rather than chemical, mainly because the chemical role of B_{12} in intermediary metabolism is unknown and therefore cannot be discussed. Techniques are presented which may be used in clinical and research laboratories for investigating B_{12}.

All of the chapters include adequate references to the literature, and the volume concludes with author and subject indexes.

EUGENE W. RICE

MONO- AND SESQUITERPENOIDS. *The Chemistry of Natural Products Series. Volume II.* *By P. de Mayo. Interscience Publishers, New York and London.* $7.50. viii + 320 pp.; ill. 1959.

This volume is a brief introduction to the chemistry of the lower molecular weight terpenoids. The Table of Contents (which seems unnecessarily brief) lists the following chapters: The Monoterpenoids, the Monocyclic Monoterpenoids, the Bicyclic Monoterpenoids I and II, and the Sesquiterpenoids I and II. The treatment is not exhaustive, but well conceived within the framework of an introductory study. The material is presented as essentially a series of "case histories"; the section on naphthenoid sesquiterpene lactones, for example, includes the proofs of structure and a number of interesting transformations of santonin, artemesin, ψ santonin, and pyrethrosin. A section on physical methods of analysis rounds out the volume. The text is profusely illustrated with line drawings. Since the odd-numbered pages are devoted solely to the illustrations, the structures of the compounds discussed are usually adjacent to the text. The treatise is recommended as an introduction to this interesting class of compounds.

EMIL H. WHITE

ORGANIC REACTIONS, *Vol. IX.*

Roger Adams, Editor-in-Chief. John Wiley & Sons, New York; Chapman & Hall, London. $12.00. viii + 468 pp. 1957.

ORGANIC REACTIONS. *Volume 10.*

Edited by Roger Adams. John Wiley & Sons, New York; Chapman & Hall, London. $12.00. viii + 563 pp. 1959.

Volumes IX and X are the latest in this series devoted to the comprehensive survey of synthetically useful organic reactions. In volume IX, the synthetic methods discussed are indicated by this listing of chapter headings: The Cleavage of Non-enolizable Ketones with Sodium Amide; The Gattermann Synthesis of Aldehydes; The Baeyer-Villiger Oxidation of Aldehydes and Ketones; The Alkylation of Esters and Nitriles; The Reaction of Halogens with Silver Salts of Carboxylic Acids; The Synthesis of β-Lactams; and The Pschorr Synthesis and Related Diazonium Ring Closure Reactions.

In volume X, the topics discussed are: The Coupling of Diazonium Salts with Aliphatic Carbon Atoms; The Japp-Klingemann Reaction; and The Michael Reaction.

In each chapter, as in the previous volumes of this series, experimental procedures are given for typical syntheses, and exhaustive tables of data are given to outline the scope of the reaction.

EMIL H. WHITE

ORGANIC SYNTHESES. *An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals. Volume 37.*

Edited by James Cason. John Wiley & Sons, New York; Chapman & Hall, London. $4.00. vii + 109 pp.; ill. 1957.

ORGANIC SYNTHESES. *An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals. Volume 38.*

Edited by John C. Sheehan. John Wiley & Sons, New York; Chapman & Hall, London. $4.00. viii + 120 pp.; ill. 1958.

ORGANIC SYNTHESES. *An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals. Volume 39.*

Edited by Max Tishler. John Wiley & Sons, New York; Chapman & Hall, London. $4.00. viii + 114 pp.; ill. 1959.

Volume 37 of this well-known series contains detailed instructions for the synthesis of 32 compounds. Of particular interest to the biochemist are syntheses of the following compounds: 2-chloronicotinonitrile, diaminouracil hydrochloride, 3-*n*-heptyl-5-cyanocytosine, nicotinamide-1-oxide, parabanic acid, and pseudopelletierine. In Volume 38, syntheses of the following compounds with some biochemical interest are reported: 2-amino-4-anilino-6-(chloromethyl)-*s*-triazine, 2-benzylaminopyridine, β-methylglutaric anhydride, and monobenzalpentaerythritol. In Volume 39, the syntheses of N-(*p*-acetylaminophenyl) rhodanine, 9,10-dihydroxystearic acid, *p*-dithiane, 2-mercapto-4-amino-5-carbethoxypyrimidine (and the 4-hydroxy derivative) are of some interest.

EMIL H. WHITE

THE HYDROGEN BOND.

By George C. Pimentel and Aubrey L. McClellan. W. H. Freeman, San Francisco and London; [Reinhold Publishing Corporation, New York]. $9.50. xii + 475 pp.; ill. 1960.

Since the hydrogen bond was first described to explain the unique properties of water in 1920, the presence of this type of bonding has been found to be rather extensive in nature. The basic structural forms of the chemical components of the living cell are greatly influenced by the hydrogen bonding of both the intra- and inter-molecular types. This book is devoted to a review of the subject, including the theoretical as well as the experimental aspects. Each chapter is introduced by a quotation from early workers in the various aspects of hydrogen bonding. The topics covered include methods of detection, both spectroscopic and nonspectroscopic, theoretical discussions, thermodynamic properties, practical systems involving this bond, and proteins and nucleic acids. The last-named chapter will be of great interest to workers in the biological field, although equally good discussions of hydrogen bonding have appeared previously. Many of the important techniques are not adequately discussed, for example, optical rotation measurements. The field of spectroscopy and its application to the study of this bond is very well covered and provides the reader with many practical suggestions in the detection of the types of hydrogen bonds. A summary is included after many of the discussions of individual topics and after most chapters. References to the original literature are provided within the text as well as reproductions of original data. These permit the reader to evaluate the data as well as the conclusions reached by the authors. The Appendix contains a list of symbols which makes the reading of the book easier than if the symbols were defined only in the text. A table in the Appendix lists the thermodynamic properties of the hydrogen bonding. One of the greatest values of the book is its bibliography of 2,242 references. An index of the joint authors who are not listed first on the papers

is also included. The subject index refers both to the bibliography and the text of the book.

The reading of this book requires some understanding of the fundamentals of physical chemistry. Although there may not be sufficient detail to satisfy some workers in particular fields, this book represents the first comprehensive text devoted to the important subject of hydrogen bonding. It will remain the primary source of information for this subject. This book may not find its way to the bookshelves of the general reader, but it will be very valuable for research specialists in physical methods of biological research.

LEOPOLD MAY

MICROBIOLOGY

Zinsser MICROBIOLOGY. *Twelfth Edition. By David T. Smith, Norman F. Conant, and 7 other contributors. Appleton - Century - Crofts, New York.* $13.00. xiv + 1026 pp; ill. 1960.

While in the eleventh edition the chapters on immunology were expanded (*Q. R. B.*, 33: 93. 1958), in the twelfth edition a new 72-page section on parasitology further widens the scope of this textbook. The content is now brought into line with the subject matter covered in most courses in medical microbiology as taught in the United States at present. In the new edition, 52 additional illustrations supplement older figures, but a number of the figures remain relatively uninstructive. The new figures are, for the most part, photographs or deal with the subject matter of the new section, and little effort has been given to develop pictorial diagrams of concepts presented in the text. The surveys of the various pathogens are complete, but routine. Most unfortunate, however, is the comparatively poor quality of the important ten introductory chapters on general bacteriology and the physiology and ecology of microorganisms. These chapters do not appear to have received concerted attention since the last edition, yet they require substantial improvement in internal organization and clarity. There is often little emphasis on important concepts, as distinct from minutiae, and no appreciation is given to the experimental background underlying the descriptive material. One concludes that, in this edition at least, Zinsser is inferior to the Rivers-Horsfall, Dubos combination (*Q. R. B.*, 34: 182. 1959), and even to Burrows (*Q. R. B.*, 35: 106. 1960) in suitability for use in medical school instruction in microbiology.

PHILIP E. HARTMAN

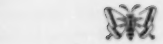
PROGRESS IN INDUSTRIAL MICROBIOLOGY. *Volume 2. Edited by D. J. D. Hockenhull. Interscience Publishers, New York.* $7.50. viii + 194 pp.; ill. 1960.

The relationships of bacteriology, statistics, engineering, and biochemistry to industrial microbiology are well illustrated in the present volume. For example, D. J. D. Hockenhull describes The Biochemistry of Streptomycin Production in an effort to present the overall picture of the fermentation, "as a unified background for further work." This goal was accomplished: your reviewer caught himself speculating about the possible effects that addition of proteinases or ureases (or inhibition of these enzymes) might have on streptomycin production. The fermentation industries are represented by two additional reviews. R. Elsworth brings together much information and experience in the area of Fermentor Design and Fermentation Control in a review which emphasizes details concerning the development of his experimental equipment, with explanations of the pitfalls encountered and means by which specific problems were solved. Reviews by D. Pearlman are always welcome, and a very succint one on the Fungal Synthesis of Citric, Fumaric and Itaconic Acids, by Perlman and C. J. Sih, appears in this book.

A review of The Lactobacilli, by J. G. Davis, encompasses information regarding the taxonomy, cytology, and physiology of these microorganisms, and serves as a well-organized catalog of references ready for easy assimilation. The Microbiological Production of Vitamin B_{12} and Sulphide from Sewage are covered by V. A. Knivett. The first subject serves as an interesting adjunct to a recent review by D. Perlman in *Advances in Applied Microbiology*, 1959. The second subject is a more extensive presentation of one area covered by the following paper by J. Postgate: Economic Activities of Sulphate-Reducing Bacteria. Postgate does a remarkable job of bringing together many diverse studies, although several sections are rather incomplete. The section on the nutrition of ruminants, for example, lacks reference to several important publications, such as those by Emery et al. (*Appl. Microbiol.*, 5: 360 and 363. 1957) and Hubert et al. (*J. Animal Sci.*, 17: 559. 1958). J. P. R. Tootill explains original solutions of Non-Linear Problems in Statistical and Mathematical Interpretation for evaluation of Michaelis constants, microbiological antibiotic recovery assays, and the analysis of counter-current distributions. The paper is not a review of the literature, but this fact does not lessen the usefulness of the material to bioanalysts.

Progress in Industrial Microbiology is much like an election-year platform: there is something for almost everybody.

PAUL A. HARTMAN



PARASITOLOGY

SYSTEMA HELMINTHUM. *The Cestodes of Vertebrates. Volume II.*

By Satyu Yamaguti. Interscience Publishers, New York and London. $90.00; (subscription $75.00). viii + 860 pp. + 70 pl. 1959.

This volume is a continuation of Satyu Yamaguti's systematic treatment of all the known helminth parasites in the world. The format is essentially the same as that in the first volume, which covered the Digenetic Trematodes of Vertebrates.

A brief introduction and a general morphological account of the cestodes occupy the first 7 pages. The main text (343 pages) consists of a classification of the cestodes, presented according to the primary divisions of their host animals, under which they are then divided by differential keys into orders, families, and genera. A diagnosis is given for each of these taxa. The type species is indicated after each generic description, and the species belonging to that genus are listed in alphabetical order. The remaining sections of this volume include a useful systematic survey of the cestodes with their definitive host relationships (15 pages), an extensive bibliography (160 pages with 3,227 references), 70 plates with 1,524 figures done by the collotype process, and an index (91 pages).

The scheme of classification presented by Yamaguti is largely the result of his own studies of helminths in Japan, which have been published in a series of papers since 1933. In addition to a number of emendations, the author has erected 3 new families, 6 new subfamilies, 31 new genera, and 6 new subgenera. The most extensive taxonomic changes are to be found in the largest and most unwieldy cyclophyllidean family Hymenolepididae. Besides following the recent revisions published in the Russian language by Spassky and his collaborators, Yamaguti has added 20 new genera of his own, bringing the total number now in this family up to 53, with 597 species recognized as valid.

Yamaguti's classification of the family Hymenolepididae involves two questionable assumptions which limit its taxonomic usefulness. First, it has been assumed that the number and arrangement of the testes are stable, particularly in those species of the subfamily Hymenolepidinae which have three or fewer testes. Previous classifications based on this concept (notably those of Cohn, 1901; Clerc, 1902, 1903; Fuhrman, 1906, 1932; Mayhew, 1925; and Lopez-Neyra, 1942) did not stand the test of workability after taxonomists began to recognize that the number and arrangement of testes were not as constant in this subfamily as was once supposed. Moreover, the results of recent investigations of morphological variation in the genus *Hymenolepis* (by Schiller, 1950, 1952, 1959; Voge, 1952; Singh, 1956; Oswald, 1957; and Freeman, 1960) have provided additional evidence that testis position is too unstable to be useful as a criterion for generic differentiation. Thus the splitting of the genus *Hymenolepis* sensu lato into a large number of new genera has served only to add to the confusion that already exists in the taxonomy of this group. It has become increasingly evident that analyses of variability are not only desirable but essential to the formulation of a sound system of classification. Until the extent of variation becomes better known for those species comprising the large number of new genera erected by Spassky et al., and by Yamaguti, it would seem advisable to retain *Hymenolepis* sensu lato for those tritesticular hymenolepidids which do not fall clearly into the few genera that are well delineated by more reliable criteria.

Second, in splitting the genus *Hymenolepis*, both Spassky and Yamaguti have assumed that a high degree of host specificity exists among the hymenolepidids. The evidence for this assumption is far from conclusive. Most of the available data concerning host specificity have been derived from statistical reports of the number of different host species in which the parasite has been found. These data are based entirely upon taxonomic works, and in many cases specific identifications are questionable because of intraspecific variability in some of the characters upon which the species concept has been established. While it is evident that related hosts tend to have related parasites, there are numerous exceptions, particularly among animals with similar habits. Until the extent of host specificity is evaluated more completely, there is little justification for its use as a major taxonomic criterion.

Systematists in general have regarded the number, size, and shape of the rostellar hooks in cestodes as being fairly constant within a species, and consequently these characters have been given considerable weight in hymenolepidid taxonomy. The results of studies on morphological variation in these characters support this concept of constancy. However, because of the similarities in rostellar hook morphology which prevail in the subfamily Hymenolepidinae, differences in hook shape have become increasingly more difficult to analyze critically. Although no satisfactory method has been devised for expressing, in precise terms, configurations of this type, carefully prepared diagrammatic illustrations have been of considerable value. In view of the taxonomic importance of these characters, it is unfortunate that, in his generic diagnoses, Yamaguti resorted to the use of such relatively meaningless terms as "sickle-shaped," "wedge-shaped," "wrench-shaped," "wrench- or wedge-shaped," "somewhat wrench-shaped," "wrench-like-shaped," "Y-shaped,"

"rosethorn-shaped," "cheliform," "spiniform," "deciduous," etc., in describing rostellar hook morphology.

The keys, of course, are artificial. My students and I have tested them on specimens belonging to a number of the smaller pseudophyllid, trypanorhynchid, and cyclophyllid taxa, and have found them to be generally satisfactory; but, in the large subfamily Hymenolepidinae, our experiences with the key to the genera have been unsuccessful. Because this key is based on the same assumptions with regard to testis arrangement and host specificity as those implicit in the generic diagnoses, it becomes unworkable as soon as one encounters the problem of morphological variability.

Although this volume does not provide for species identification, the information presented along with the specific names listed under each genus does facilitate the location of references to the original sources in the literature.

The illustrations leave much to be desired. The figures have been reduced to such an extent that often there is a complete loss of important details. Usually there is a figure to illustrate a species of each genus and, with a few exceptions, the type species is illustrated. There are relatively few typographical errors.

While there is unlikely to be complete agreement on many aspects of Yamaguti's system of classification, it must be recognized that this work, because of the thoroughness with which the author has compiled and organized an extensive and widely scattered literature, is, in itself, a major contribution to the field of parasitology. In my opinion, this volume will be invaluable to the cestode taxonomist and an important reference for all helminth parasitologists; but, because of the prohibitive cost, it seems doubtful that it will be commonly found in the private libraries either of students or their professors.

EVERETT L. SCHILLER

HEALTH AND DISEASE

ANNUAL REVIEW OF MEDICINE. *Volume 11. Editor: David A. Rytand; associate editor: William P. Creger. Annual Reviews, Palo Alto.* $7.00. viii + 453 pp.; ill. 1960.

Twenty-three reviews are included in this volume. A sampling is as follows: Hepatic coma (Sherlock); Arterial hypertension (Sokolow and Sanazaro); pulmonary hypertension (Liebow); Acute renal failure (Merrill); the L. E. cell phenomenon (Holman); and Congenital enzyme defects (Gerrard and Marko). As usual, this is a useful series of reviews. Extensive bibliographies and full author and subject indices are provided. In addition, this volume contains a cumulative index of the reviews contained in Volumes 1 to 11.

VICTOR A. MCKUSICK

METHODS IN MEDICAL RESEARCH. *Volume 8. Edited by H. D. Bruner. The Year Book Publishers, Chicago.* $9.75. xiv + 368 pp.; ill. 1960.

Volume 8 of the series is divided into three sections, each with its own editor and group of authors: Life History of the Erythrocyte (W. S. Root, ed.); Measurement of Responses of Involuntary Muscle (A. M. Lands, ed.); and Peripheral Blood Flow Measurement (H. D. Bruner, ed.)

Each section is made up of a series of articles describing in a very detailed fashion the techniques used in current research in that particular field. In the section on the life history of the erythrocyte, for example, the methods are outlined for working on the bone marrow in vivo and in tissue culture, for estimating the rate of formation of the erythrocytes, for measuring the red blood cell volume, for determining its life span, and for determining the turnover rate. Each method is described with the necessary minutiae to get it to work. One unusual feature of the book is the way in which most of the articles are followed by a short comment made by a competent referee, so that the user of the book is furnished with a very critical evaluation of the methods described. The book is written on a practical level that should make it useful to people working in purely clinical laboratories as well as those engaged in basic research. One hopes that future volumes in this series will do as well in respect to their subjects as this volume, and the earlier ones in this series, have done with theirs.

M. L. WOLBARSHT

CANADIAN CANCER CONFERENCE. *Proceedings of the Third Cancer Research Conference, Honey Harbour, Ontario, June 17–21, 1958. Volume 3. Edited by R. W. Begg. Academic Press, New York and London.* $12.00. xiv + 461 pp.; ill. 1959.

The proceedings of this conference represent a continuation of previous meetings held in 1954 and 1956. Volume 3 again accurately presents the objective of the conferences: to review the various fields of cancer research. In Volume I basic problems were explored: Experimental Tumors, Tumor-Host Relations, Enzymes, Ionizing Radiations. In Volume II: The Cell, Leukemia and Chemotherapy, Hormones and Cancer, Immunity and Basic Mechanisms. In Volume III a similar plan has been followed. Four main subjects are discussed: Nucleic

Acids; Genetics; Viruses and Tumors; and the Biology of Cancer. Each paper deals with some aspect of basic cancer biology. Like the preceding volumes, Volume III is an excellent reference work and review of the present state of basic cancer research.

ROBERT G. CHAMBERS

ANTIBIOTICS ANNUAL, *1959–1960.*

Henry Welch, chairman; under the Editorial Direction of Félix Martí-Ibáñez. Antibiotica, New York. $15.00. xx + 1034 pp.; ill. 1960.

This volume contains the papers presented at the Seventh Annual Symposium on Antibiotics held in 1959 in Washington, D. C. In addition to general review papers of an introductory character, there are 132 research papers largely concerned with new antibiotic agents. A complete subject and author index is included.

C. JELLEFF CARR

CELLULAR AND HUMORAL ASPECTS OF THE HYPERSENSITIVE STATES. *A Symposium Held at the New York Academy of Medicine.*

Edited by H. Sherwood Lawrence. A Hoeber-Harper Book, New York. $18.00. xvi + 667 pp.; ill. 1959.

This most interesting symposium on the broad and controversial subject of hypersensitivity has drawn together an excellent and distinguished group of contributors. Although each contributor's approach to the subject is unique, he never forgets that he is discussing the hypersensitive state(s). This manifold approach permits inclusion of a variety of related topics, and thereby makes the book especially valuable for reference.

In each of the 18 chapters the author(s) begins with a general description of past work and ideas; he then offers in lucid form his own arguments and data on some aspect of hypersensitivity. For example, in the opening chapter J. H. Humphrey presents a clear, detailed report on the Biochemical Aspects of Reactions in Hypersensitive Responses. Similarly, Herman Eisen writes an excellent account of classical and contemporary work, especially his own, in the chapter entitled Hypersensitivity to Simple Chemicals. Both of these chapters are followed by discussion sections which contain pertinent comments and references to published and unpublished work. A warning against "anthropocentricity" is sounded by Merril Chase, who also asks the experimenter to take note of genetic constitution in Models for Hypersensitive Studies. In the next chapter H. Sherwood Lawrence reports on a series of experiments in regard to the nature, location, and mode of action of "transfer factor." Chapter 10 and its subsequent discussion section afford a fine example of how the study of a pathological condition, agammaglobulinemia, can provide evidence about the biochemical, cytological, and genetic control of antibody synthesis. In the closing chapter, Jacques Monod presents a provocative comparison of induced enzyme and antibody formation.

This volume seems admirably to accomplish its avowed purpose as set forth in the Preface, namely, "to encompass critically the diverse approaches to this rapidly changing and expanding field for the student, investigator and the physician." Unfortunately, a financial hypersensitivity to the high price of this book will probably prevent its acquisition by members of the first group named. Perhaps Federal aid to education should include financial assistance for paperback editions of valuable but expensive books such as this one.

MICHAEL CARSIOTIS

PSYCHOLOGY AND ANIMAL BEHAVIOR

LANGUAGE DEVELOPMENT AND LANGUAGE DISORDERS: *A Compendium of Lectures. Monogr. Soc. Res. Child. Developm., Vol. 25, No. 3.*

Compiled by Nancy E. Wood. Child Development Publications, Purdue University, Lafayette. $2.75 (paper). 95 pp. 1960.

HUMAN BIOLOGY

PEOPLE AND PLACES.

By Margaret Mead; illustrated by W. T. Mars and Jan Fairservis. The World Publishing Company, Cleveland and New York. $4.95. 318 pp.; ill. 1959.

People and Places is timely and thought-provoking. The reader is helped to view problems that face our world in better perspective.

The first three chapters serve as orientation. They relate how men have learned about themselves and one another, and how an anthropologist goes about his work of studying people and their cultures, past and present. In the next 6 chapters 5 very different cultural groups are described. Margaret Mead discusses at length the Eskimos, and Indians of the Plains, the Ashauti of West Africa, the Balinese, and the Minoans of Crete.

The book's last section is a summation. One chapter deals with the basic concepts all people share, no matter how different their cultures. Because such ideas are common to all living people, they "can be said to be as firmly the inheritance of the human race as are those things which we . . . inherit

biologically from our ancestors." Other ideas and inventions, not shared by all groups, might be lost entirely through the destruction of those who know about them. Only when an idea or invention becomes common knowledge is it a part of human inheritance. The second chapter of the conclusion discusses questions that have arisen in all cultures, and the very different answers and solutions arrived at by different societies.

The last chapter, The Steps We Know Must Be Taken, is the most challenging of all. It represents an anthropologist's analysis of today's problems, and suggests approaches to their solution. The book is well worth reading, both for children of high school age and for adults. It includes a long (3-page) list of Books for Further Reading as well as a 4-page list of Sources.

MARY DEMEREC

HANDBOOK OF AGING AND THE INDIVIDUAL. *Psychological and Biological Aspects.*

Edited by James E. Birren. The University of Chicago Press, Chicago. $12.50. xii + 939 pp.; ill. 1959.

Although the title of this almost encyclopedic work is somewhat misleading, it is, by and large, a creditable effort which should be of considerable usefulness to gerontologists, particularly those in the psychobiological areas of the field. The volume could more aptly, perhaps, be entitled "Essays on Cellular and Behavioral Aspects of Aging." Certain of these articles are truly outstanding, most are far above average in the field, and a few appeared to hit wide of the mark.

Among the outstanding articles are those of Birren on Principles of Research on Aging; an essay of Maria Reichenbach and Ruth Anna Mathers on The Place of Time and Aging in the Natural Sciences and Scientific Philosophy, which may well be regarded as a classically excellent survey of time from the physical standpoint; an outstanding, critical review of the Morphology of the Aging Nervous System, by William Bondareff; a wide-ranging discussion of Biological Periodicities, Mathematical Biology and Aging, by Herbert Landahl; and a stimulating discussion of Work and Occupational Skills, by Ross A. McFarland and Brian O'Doherty.

Clearly, less effort was expended in reviewing the biology of the process. Lansing's chapter is a brief, readable, but not altogether critical, survey.

Hardin B. Jones' chapter contains a rearranged restatement of many of the arguments set forth in his earlier papers. However interesting the many relationships between disease, mortality, and cohorts may be, a review article of this sort might well state more explicitly the difference between conjecture and observation, and could well afford to present theories and deductions in a more rigorously formal manner than the rather loose and inconsecutive style that occasionally supervenes. Some statements of questionable nature may be quoted for purposes of illustration: "The force of mortality, nearly constant from postadolescence to senescence, presents a powerful argument for the concept of a continuous decay of vitality . . . ." (p. 344). Again, "Among examples of evidence supporting this theory are radiation effects, in that morbidity induced by radiation exposure induces a proportional degree of aging over a wide range of exposure." (p. 347). The errors consist in the former case of the misuse of the term "force of mortality" and in the latter of the use of a secondary assumption (that radiation causes aging) to support another hypothesis (the hypothesis of the autocatalytic nature of impairment).

Similarly, consider the comments of Lansing on the turnover of protoplasmic constituents:

> Quite apart from the capacity of duplication of whole organisms by reproduction and cell duplication by mitosis, there is the truly remarkable ability of protoplasm to renew itself as it is consumed by vital activities. I have been perplexed and continue to be perplexed by the seeming anomaly between this self-synthetic capacity of protoplasm and senescence. If protoplasm is in a continual state of renewal, how can it wear out?
>
> It is this essential attribute of life that renders inappropriate the analogies between the wearing-out of non-living systems and the senescence of living organisms. Shoes, piston rings, and automobile tires wear out because of sustained friction; rubber bands oxidize and become inelastic with the passage of time; and clocks run down. None of these failures due to use and the passage of time is analogous to the senescence of living things. The latter should, at least on a theoretical basis, contain ever vigorous protoplasm. (pp. 121–123).

There is patently no sound theoretical basis for the last statement. The Schoenheimer experiments have largely been superseded by the discovery of several large non-turning-over fractions in animals [see Thompson and Ballou, *J. Biol. Chem.*, 223: 795–809. 1956] and various chemical and physical analogies may have considerable validity. Certainly teeth wear out because of friction; the change in elasticity of connective tissue may well be analogous to the aging of rubber.

All in all, however, this volume makes a valuable addition to a reference library or the bookshelves of the curious.

B. L. STREHLER

HANDBOOK OF SOCIAL GERONTOLOGY. *Societal Aspects of Aging.*

Edited by Clark Tibbitts. The University of Chicago Press, Chicago. $10.00. xx + 770 pp. 1960.

This book will be of special interest to the biologist, not as a volume furthering his knowledge in the biological sciences, but as a book with much information that will be of value in assessing certain important social problems of our times, namely, "What is the effect of an aging population on our culture?"—and "How can the needs of an older population be met?" This book is the second of a trilogy, the first of which (*Handbook of Aging and the Individual; Psychological and Biological Aspects*, edited by J. E. Birren) appeared last year, and the third (*Aging in Western Societies; a Survey of Social Gerontology*, edited by E. W. Burgess) is scheduled for publication in 1961. All three volumes represent the work of a committee appointed by the Gerontological Society in 1955 for the purpose of considering the pressing question of how to increase the number of university and college teachers equipped to train others in the psychological and sociological aspects of aging. Prepared by 23 authors, the volume presents statistics on the age structure of the population and makes predictions for the future, some of which dispel the gloom of earlier projections by showing the impact of a rising birth rate on the age distribution of the population. Chapters on the economic problems of an aging population offer background data for serious thought concerning our future policies with regard to retirement and employment. The issue is raised with respect to forced retirement at age 65—or at 60. Other topics covered by the book include aging in different societies, the health status of aging people, income maintenance in the aged, employment and retirement, family relationships, housing, religion, the role of governmental and voluntary agencies in dealing with the problems of the aged, and the uses of leisure time. This volume focuses attention on the importance of social factors in permitting the phenomena of senescence to appear in the human. Without the protective devices that have evolved with our culture, senescence would probably be impossible. All chapters are well documented with references to the literature in this field, but a brief summary of each author's general position and conclusions would have been useful to the reader. The book is well indexed with respect to both authors and subjects. Its 700 pages certainly represent a significant contribution to the field of aging, and the volume undoubtedly will serve as a primary reference volume for some time to come.

N. W. SHOCK

FALLOUT. *A Study of Superbombs, Strontium 90, and Survival.*

Edited by John M. Fowler. Basic Books, New York. $5.50. xii + 235 pp.; ill. 1960.

In a democracy, it is essential that the electorate be informed and knowledgeable concerning matters of public interest requiring long-term policy decisions. Our mushrooming technology has rendered the problem of informing the public acute in the extreme. Epitomizing this general problem have been the long and at times heated public discussions of nuclear weapons tests and their possible biological consequences. There has been a real need for a compilation of the underlying facts in a form intelligible to the layman.

The two Congressional Hearings on this subject did not meet the need. Excellent Hearings though they were, impartial and complete, they left behind large volumes of collected testimony and documents which require heroic efforts, even on the part of competent scientists, to digest and to understand.

Fowler and his associates in the edited volume, *Fallout*, have attempted the almost impossible task of presenting the facts in a less formidable form. The volume suffers from compromise. However, it is probably impossible to avoid such compromise. How can one be brief and yet complete, accurate without qualification, definitive, and unbiased? Despite these difficulties, Fowler and his contributors have succeeded remarkably well. The literary style is good. Subject matter which could easily make for dull reading is interestingly presented. Proponents of nuclear tests are conspicuously absent from the list of contributors. Even so, the authors have recognized their responsibility to inform rather than convince and, to a man, have been candidly honest in labeling personal opinion (when they felt compelled to speak their mind) as opinion.

To summarize, this volume, though far from perfect, represents the best, most understandable, authoritative compilation yet to appear on the subject. It should be considered as required reading, if not for the layman, for every technically trained person to whom the layman must turn for assistance.

The contents are as follows: Foreward (Adlai E. Stevenson); Introduction (John M. Fowler); The Bombs and their Products (John M. Fowler); The Global Pattern of Fallout (Lester Machta & Robert J. List); From Bomb to Man (W. O. Caster); The Rising Level of Fallout (J. M. Fowler); Biological Effects of Radiation (Walter R. Guild); Radiation and Future Generations (James F. Crow); Radiation Accidents (Gould A. Andrews); Protection and Treatment (Jack Schubert); Civil Defense (Chet Holifield); Detection of Bomb Tests (Arthur H. Rosenfeld); Nuclear War (Ralph E. Lapp); and National Survival (J. M. Fowler). There are appendices dealing with Fundamentals of Radiation, Fission and Fusion, a List of Nuclear Explosions, and estimated Casualties in a Nuclear Attack. The volume is also provided with a glossary and an index.

W. F. NEUMAN

BIOMETRY

REGRESSION ANALYSIS.

By E. J. Williams. John Wiley & Sons, New York; Chapman & Hall, London. $7.50. x + 214 pp. 1959.

This book is a much needed compendium of the classical techniques of regression analysis. It is addressed primarily to the research worker in the physical sciences and is concerned with the applications of regression methods to examples in this field. Many of the topics are brought together and illustrated for the practitioner for the first time within a single volume. Although most of the theory underlying the applications is intentionally omitted and complicated mathematical concepts are avoided, the author has been careful throughout to emphasize the conditions under which the various techniques are both relevant and valid, and he has been able to bring his considerable knowledge and experience to bear on this point. It is unfortunate that the statistical arguments are given in the language of fiducial probability rather than in terms of confidence interval statement and, for that reason, may cause unnecessary confusion for many readers.

The contents are as follows: Introduction; Linear Regression; Multiple and Polynomial Regression; Regression Equations Requiring Iterative Calculation; Choice Among Regression Formulas; Estimation from the Regression Equation; The Analysis of Covariance; The Treatment of Heterogeneous Data; Simultaneous Regression Equations; Discriminant Functions; Functional Relations; References; and Index.

EDWARD B. PERRIN

METHODS OF CORRELATION AND REGRESSION ANALYSIS, *Linear and Curvilinear. Third Edition.*

By Mordecai Ezekiel and Karl A. Fox. John Wiley & Sons, New York; Chapman & Hall, London. $10.95. xvi + 548 pp.; ill. 1959.

Two previous editions (1930, 1941) of this well-known book were entitled *Methods of Correlation Analysis* by M. Ezekiel, and the present volume is the third edition, revised with the help of K. A. Fox. The new title indicates that the emphasis has shifted from correlation to regression. Hence, a new chapter (Chap. 24) on the solution of simultaneous equations has been added. The relation between the analysis of variance and regression problems has also been treated in more detail.

The numerical illustrations of methodology and the discussions of results of analysis are, as in previous editions, mostly around examples taken from agricultural economics, a field in which the authors have long experience and speak with authority. For students of this field, the book will serve its purpose admirably. General students and research workers who want to learn the techniques of correlation and regression methods, however, will find the data on corn and cows not too exciting. The book is bulky and slow-moving, and could be streamlined and condensed considerably. For instance, the discussion of the meaning of a regression coefficient and its standard error has been repeated many times in various chapters.

C. C. LI

DE OMNIBUS REBUS ET QUIBUSDAM ALIIS

GRAND CANYON. *Today and All Its Yesterdays.*

By Joseph Wood Krutch. William Sloane Associates, New York. $5.00. xii + 276 pp. + 1 pl. 1958.

Joseph Wood Krutch visited the Grand Canyon for the first time twenty years ago. He was so overcome by its beauty, grandeur, and mystery that he has returned many times to live near the canyon, explore it, and study the geology, animal and plant life, and history of the region. This book is the outcome of these studies, and the author's proprietary interest and love for the Grand Canyon area give it a special flavor and charm.

The author discusses the various theories of the origin of the canyon and the history of the rocks which comprise its walls. He gives directions to reach spots along the canyon in which one can find complete solitude and views which have been seldom, if ever, photographed. Stories about the discoverers of the canyon, its early explorers, people who have lived in the region and others who have studied it, add to the interest of the book.

Krutch closes with a powerful, moving plea for the preservation of the existing National Wilderness areas. He says: "The generation now living may very well be that which will make the irrevocable decision whether or not America will continue to be for centuries to come the one great nation which had the foresight to preserve an important part of its heritage."

MARY DEMEREC

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